TRANSACTIONS

OF THE

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

Sixty-fourth Annual Meeting held at

Hot Springs, Virginia

May 6, 7 and 8, 1953

Volume XLV

Published for the Association by the
Williams and Wilkins Co.
Baltimore
1954

OCT 8 '54 U. OF M. BINDERY

S610.6
Am3E

OFFICERS, 1952–1953

President

A. J. SCHOLL, M.D., Los Angeles, Calif.

Vice-President

VINCENT J. O'CONOR, M.D., Chicago, Ill.

Secretary-Treasurer

NORRIS J. HECKEL, M.D., Chicago, Ill.

Members of the Council

CHARLES C. HIGGINS, M.D., Cleveland, Ohio

C. P. HOWZE, M.D., Washington, D. C.

The President
The Vice-President } Ex-officio
The Secretary

MEMBERS

HONORARY MEMBERS

DR. J. DELLINGER BARNEY (1912), 374 Marlborough Street, Boston, Mass.
DR. WILLIAM F. BRAASCH (1913), Mayo Clinic, 102 Second Avenue, S.W., Rochester, Minn.
DR. JOHN H. CUNNINGHAM (1906), 53 Seaver Street, Brookline, Mass.
DR. FRANK HINMAN (1920), 74 Atherton Ave., Atherton, Calif.
DR. ALFRED T. OSGOOD (1906), 225 E. 73rd St., New York, N. Y.
DR. LOUIS E. SCHMIDT (1903), 316 Ruder St., Wausau, Wis.
DR. ALFRED C. WOOD (1900), 2035 Walnut St., Philadelphia, Penna.

CORRESPONDING MEMBERS

DR. DAVID BAND (1953), 19 Douglas Crescent, Edinborough 12, Scotland
PROF. MAURICE Chevassu (1953), 1 Avenue de Tourville, Paris 7, France
PROF. BERNARD FEY (1953), 54 Avenue de New York, Paris 16, France
DR. W. H. GALBRAITH (1953), 7 Woodside Terrace, Glasgow C. 3, Scotland
MR. KEITH KIRKLAND (1948), 137 Macquarie St., Sydney, Australia.
DR. T. J. MILLIN (1953), 31 Queen's Gate, London, S.W. 7, England
MR. HENRY MORTENSEN (1948), 33 Collins St., Melbourne, Australia.
DR. E. W. RICHES (1953), 22 Weymouth St., London W 1, England
DR. EGON WILDBOLZ (1953), 25 Sulgeneckstrasse, Berne, Switzerland

FELLOWS

DR. MONTAGUE BOYD (1921), 563 Capitol Ave., S. W., Atlanta, Ga.
DR. HERMON C. BUMPUS (1923), 1 Upland Road, Duxbury, Mass.
DR. C. E. BURFORD (1926), 812 Olive St., St. Louis, Mo.
DR. ARTHUR B. CECIL (1921), 1136 West Sixth St., Los Angeles, Calif.
DR. J. A. C. COLSTON (1921), 1201 North Calvert St., Baltimore, Md.
DR. JOHN L. CRENSHAW (1924), 832-10½ St., S.W., Rochester, Minn.

U. OF M. BINDERY
OCT 8 '54
1471537

Dr. Harry Culver (1924), 7 West Madison St., Chicago, Ill.
Dr. David M. Davis (1939), 255 South 17th St., Philadelphia, Penna.
Dr. Edwin Davis (1922), 107 South 17th St., Omaha, Neb.
Dr. Clyde L. Deming (1928), 789 Howard Ave., New Haven, Conn.
Dr. Homer G. Fuller (1920), 2400 Sixteenth St., Washington, D. C.
Dr. Roger C. Graves (1924), 12 Bay State Road, Boston, Mass.
Dr. Homer G. Hamer (1923), 1711 North Capitol Ave., Indianapolis, Ind.
Dr. Alexander B. Hepler (1936), Route 1, Box 290, Port Blakely, Wash.
Dr. Leon Herman (1933), 136 So. 16th St., Philadelphia, Penna.
Dr. George F. Hoch (1940), 115 East 61st St., New York, N. Y.
Dr. T. Leon Howard (1936), 1612 Tremont Place, Denver, Colo.
Dr. Thomas F. Laurie (1922), 749 S. Warren St., Syracuse, N. Y.
Dr. George R. Livermore (1922), 248 Madison Ave., Memphis, Tenn.
Dr. Henry O. Mertz (1930), 1711 North Capitol Ave., Indianapolis, Ind.
Dr. Edward J. McCague (1934), Mercy Hospital, Pittsburgh, Penna.
Dr. Joseph F. McCarthy (1924), 353 West 57th St., New York, N. Y.
Dr. J. C. McClelland (1934), 170 St. George St., Toronto, Canada.
Dr. Clarence R. O'Crowley (1935), 31 Lincoln Park, Newark, N. J.
Dr. John K. Ormond (1939), Miraj Medical Center, Miraj, India
Dr. A. H. Paine (1922), 277 Alexander St., Rochester, N. Y.
Dr. Robin Pearse (1934), 170 St. George St., Toronto, Ont., Canada.
Dr. George G. Smith (1916), 1101 Beacon St., Brookline, Mass.
Dr. Alexander R. Stevens (1916), Alstead Center, N. H.
Dr. William E. Stevens (1930), 2655 Filbert St., San Francisco, Calif.
Dr. Gilbert J. Thomas (1923), 2200 Santa Monica Blvd., Santa Monica, Calif.
Dr. W. H. Toulson (1938), 101 W. Read St., Baltimore, Md.
Dr. William P. Willard (1916), 2741 Divisadero St., San Francisco, Calif.

ACTIVE MEMBERS

Dr. Carl Aberhart (1948), 1012 Medical Arts Bldg., Toronto 5, Canada.
Dr. William J. Baker (1940), 7 West Madison St., Chicago, Illinois.
Dr. Edgar Burns (1944), 3503 Prytania St., New Orleans, La.
Dr. George F. Cahill (1935), 121 East 60th St., New York, N. Y.
Dr. Edward W. Campbell (1944), 136 S. 16th St., Philadelphia, Penna.
Dr. Meredith F. Campbell (1941), 140 East 54th St., New York, N. Y.
Dr. Grayson Carroll (1950), 539 N. Grand Blvd., St. Louis, Mo.
Dr. Donald Charnock (1949), 727 W. Seventh St., Los Angeles 14, Calif.
Dr. Richard Chute (1947), 203 Commonwealth Ave., Boston 16, Mass.
Dr. Fletcher H. Colby (1931), 262 Beacon St., Boston, Mass.
Dr. C. D. Creevy (1939), 412 Delaware St., Minneapolis 14, Minn.
Dr. Ormond S. Culp (1948), Mayo Clinic, Rochester, Minn.
Dr. Archie L. Dean, Jr. (1935), 30 East 40th St., New York, N. Y.
Dr. John E. Dees (1953), Duke Hsopital, Durham, N. C.
Dr. Austin I. Dodson (1937), Medical Arts Bldg., Richmond, Va.
Dr. John L. Emmett (1944), Mayo Clinic, 102 Second Ave., Rochester, Minn.
Dr. Wm. J. Engel (1937), 2020 East 93rd St., Cleveland, Ohio
Dr. George W. Fish (1938), 180 Ft. Washington Ave., New York 32, N. Y.
Dr. Thomas E. Gibson (1947), 450 Sutter St., San Francisco, Calif.
Dr. B. H. Hager (1930), 445 Kelton Ave., Los Angeles 24, Calif.
Dr. Frank C. Hamm (1942), 80 Hanson Place, Brooklyn 17, N. Y.
Dr. John R. Hand (1952), 4915 S. W. Patton Rd., Portland, Ore.
Dr. J. Hartwell Harrison (1951), Peter Bent Brigham Hospital, Boston Mass.
Dr. Norris J. Heckel (1938), 122 S. Michigan Ave., Chicago 3, Ill.
Dr. William P. Herbst, Jr. (1940), 1801 Eye St., N. W., Washington, D. C.
Dr. Daniel Riggs Higbee (1950), 1612 Tremont Pl., Denver, Colo.
Dr. Charles C. Higgins (1933), 2020 East 93rd St., Cleveland, Ohio
Dr. Robert S. Hotchkiss (1948), 65 E. 66th St., New York City 21, N. Y.
Dr. C. P. Howze (1934), 1150 Connecticut Ave., N. W., Washington, D. C.
Dr. P. Boland Hughes (1942), 136 S. 16th St., Philadelphia, Penna.
Dr. Hugh Judge Jewett (1943), 1201 N. Calvert St., Baltimore, Md.
Dr. Joseph H. Kiefer (1950), 25 E. Washington St., Chicago, Ill.
Dr. Willoughby Kittredge (1953), 3503 Prytania St., New Orleans, La.
Dr. John K. Lattimer (1953), 160 Cabrini Boulevard, New York, N. Y.
Dr. Wyland F. Leadbetter (1948), 30 Bennet St., Boston 11, Mass.
Dr. Robert Lich, Jr. (1951), 801 Heyburn Bldg., Louisville, Ky.
Dr. Ben D. Massey (1944), 112 N. Madison Ave., Pasadena, Calif.
Dr. Thomas D. Moore (1946), 899 Madison Ave., Memphis 3, Tenn.
Dr. Samuel A. MacDonald (1951), 1414 Drummond St., Montreal, Canada

Dr. John T. MacLean (1951), 305 Medical Arts Bldg., Montreal, Canada
Dr. Reed M. Nesbit (1936), 1313 E. Ann St., Ann Arbor, Mich.
Dr. Vincent J. O'Conor (1926), 720 N. Michigan Ave., Chicago, Ill.
Dr. Louis Orr, Jr. (1941), 307 S. Orange Ave., Orlando, Fla.
Dr. John F. Patton, (1949) (Col. MC), Fitzsimmons Army Hospital, Denver, Colo
Dr. George C. Prather (1938), 1180 Beacon St., Brookline 46, Mass.
Dr. James T. Priestley (1941), 102 Second Ave., S. W., Rochester, Minn.
Dr. John N. Robinson (1947), 180 Ft. Washington Ave., New York 32, N. Y.
Dr. Carl Rusche (1937), 906 Taft Bldg., Hollywood, Calif.
Dr. James Clyde Sargent (1951), 324 E. Wisconsin Ave., Milwaukee, Wis.
Dr. A. J. Scholl (1926), 1930 Wilshire Blvd., Los Angeles, Calif.
Dr. William Wallace Scott (1951), 601 N. Broadway, Baltimore, Md.
Dr. Winfield W. Scott (1949), 277 Alexander St., Rochester, N. Y.
Dr. Fedor L. Senger (1944), 142 Joralemon St., Brooklyn, N. Y.
Dr. Ira Sisk (1929), 1 So. Pinckney St., Madison, Wis.
Dr. Emerson C. Smith (1941), 1390 Sherbroke St., W., Montreal, Que, Canada.
Dr. Parke G. Smith (1939), 1714 Biscayne Blvd., Miami, Fla.
Dr. Howard I. Suby (1950), 262 Beacon St., Boston, Mass.
Dr. John A. Taylor (1943), 2 East 54th St., New York, N. Y.
Dr. Gershom J. Thompson (1946), 102 Second Ave., S. W., Rochester, Minn.
Dr. Wm. I. Valk (1953), 5506 Aberdeen Road, Kansas City, Kansas
Dr. Samuel A. Vest (1950), University of Virginia Hospital, Charlottesville, Va.
Dr. John B. Wear (1937), 1 S. Pinckney St., Madison, Wis.
Dr. Henry M. Weyrauch (1952), 384 Post St., San Francisco, Calif.
Dr William Niles Wishard, Jr. (1939), 1711 N. Captiol Ave., Indianapolis, Ind

CONTENTS

Obituaries:
Linwood Dickens Keyser 1
David Wallace MacKenzie 3
William Carter Quinby 5
Uterovesical Fistula with Fetal Parts Presenting in External Urethral Meatus. M. H. Nourse and W. N. Wishard, Jr. 8
Urethral Stricture Following Transurethral Resection Prevented by Internal Urethrotomy: Preliminary Report of Experience with Otis Urethrotome. J. L. Emmett and J. R. Winterringer 12

Discussion

Results Obtained by Endocrine Control Therapy Followed by Radical Perineal Prostatectomy in Advanced Carcinoma of Prostate. Winfield W. Scott 27
Appraisal of Present Methods of Treatment of Advanced Prostatic Cancer. William W. Scott 39
Late Results of Bilateral Adrenalectomy for Advanced Carcinoma of Prostate Gland. W. J. Baker 43
Treatment of Prostatic Carcinoma with Radioactive Colloidal Chromic Phosphate. Carl Rusche and H. L. Jaffe 48
Intraprostatic Infections of Radioactive Colloids: II. Distribution within the Prostate and Tissue Changes Following Injection in Dog. G. J. Bulkley, J. A. Cooper and V. J. O'Conor 57

Discussion

Schwannomas. C. L. Deming and H. R. Newman 75

Discussion

Electromyography of Urinary Bladder. S. A. Vest and E. L. Corey 84
Antibiotic Therapy of Urinary Tuberculosis: An Interval Report of Six Years' Experience. R. M. Nesbit and C. C. MacKinney 88

Discussion

Pathogenesis of Renal Failure. J. T. MacLean 99
Dialysis in Treatment of Uremia: Artificial Kidney and Peritoneal Lavage. W. J. Kolff and C. C. Higgins 110

Discussion

Bilateral Concomitant Seminoma. A. I. Dodson and J. W. Hooper, Jr. 136
A True Hermaphrodite. A. B. Cecil 140

Discussion

Renal Function Studies in Polycystic Disease of Kidney: Preliminary Report. J. F. Patton and N. S. Bricker 149
Retropubic Prostatectomy: Review of 678 Patients. Robert Lich, Jr. 157
Prostatectomy, Mortality and Morbidity. S. A. MacDonald 162
Avoiding the Poor Results in Transurethral Prostatectomy. H. M. Weyrauch and M. L. Rosenberg 166
Importance of Frozen Sections in Evaluating Prostatic Nodules. O. S. Culp and J. R. McDonald 180
Use of Solusponge in Prostatic Surgery. J. N. Robinson 187

Discussion

OBITUARIES

LINWOOD DICKENS KEYSER

Linwood Dickens Keyser was born in Victoria, Texas, September 26, 1893. He came to the University of Virginia for his formal education and received a Bachelor of Arts Degree in 1914. Four years later he received his M.D. degree from the Johns Hopkins University and in 1921 received a Master of Science from the University of Minnesota. Following graduation from Medical School he was an intern in the Johns Hopkins Hospital and later Assistant Resident of Surgery at the Peter Bent Brigham Hospital in Boston. He was Resident Surgeon for a period at the New York Post Graduate Hospital and in 1920 went to the Mayo Clinic as a Fellow in Pathology and Surgery where he stayed for three years. In 1923 he came to Roanoke, Virginia, where he was engaged in the successful practice of Surgery and Urology. After his formal postgraduate training he showed a particular interest in the then newer laboratory aspects of medicine and was Director of Laboratories at the Roanoke Hospital. All of us are aware of his contributions to the problem of stone formation which began early in his career while at the Mayo Clinic. Practically all urologists at this time only interested themselves in the techniques of extracting stones. Our departed member, Linwood Keyser, had a more thoughtful and curious mind and continued throughout his life to muse upon the more fundamental processes involved with stone formation. I think it is of particular significance that Linwood continued the investigation of the chemical nature of stones even though he practiced in a relatively small city which did not have the advantages of a large teaching medical center. There is no question but that he had a sincere desire to contribute to medical science during his lifetime. I have looked over his bibliography and it constitutes 58 excellent articles on various urologic subjects, many of which reflected his experimental turn of mind. As an example of his initiative he had gained free access to the chemical department at V.P.I., where he was embarking on experiments exploring the nature of urinary calculi at the time of his death. As to his scientific approach I note that his last paper in press is entitled "Biochemical Studies in Relation to Calculus Disease of the Urinary Tract, with Special Reference to Calcium-Phosphorus Metabolism". One would expect this sort of contribution to emanate from centers of academic medicine.

Linwood was a member of some 20-odd societies and civic organizations among which was the Society of Sigmi Xi, the Virginia Academy of Science and the American Association for the Advancement of Science. He was president at the time of his death of the Mid-Atlantic Section of the American Urological Association.

There is little that I could tell you about Linwood from a personal standpoint, as many of you have known him longer than I over the years. He was the type of man who had a deep sense of devotion. This is exemplified by two main motivating forces in his life, the first of which was his mother to whom he devoted practically all his adult life in caring for her invalidism. In pursuance of this

devotion he did not marry. His second devoted object was purely medicine and in the main Urology. I understand that beyond these two he had little time for other hobbies or diversions. One striking aspect of his personality was that he was one of our members who showed no degree of contentiousness in his make-up and therefore had few enemies at home or abroad.

Our society has therefore lost an investigative urologist, a devoted member, and one who had given his best to the advancement of Urology within the limitations of the environment in which he found himself. I am sure that each of us has lost a personal friend.

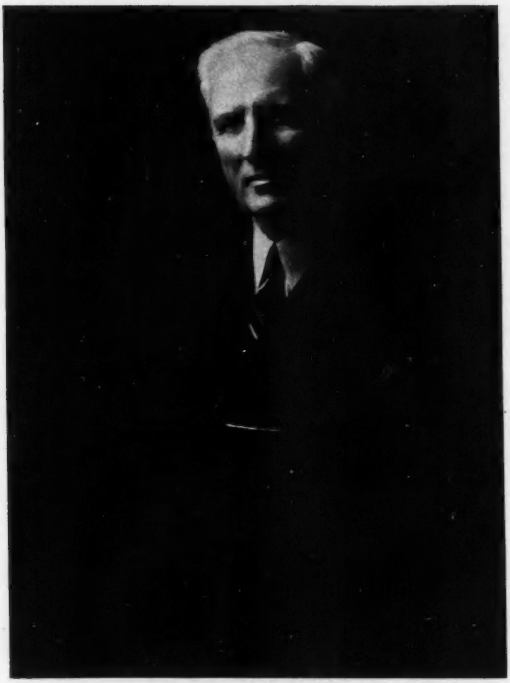
SAMUEL A. VEST

DAVID WALLACE MACKENZIE

It is with deep regret that the members of the American Association of Genito-Urinary Surgeons will note the passing of one of their distinguished members, David Wallace MacKenzie, on December 23, 1952.

David Wallace MacKenzie, B.A., M.D., F.A.C.S., F.R.C.S(C), F.R.S.Med. (Eng.), graduated in medicine from Cornell University in 1904 and received his urological training at the Bellevue Hospital. In 1916 Dr. MacKenzie was appointed urologist to the Royal Victoria Hospital in Montreal. There he established a department of Urology. In 1923 he was promoted to Urologist-in-Chief at the Royal Victoria Hospital and made Clinical Professor of Urology at McGill University.

The members of this Association will remember David Wallace MacKenzie as a gentle man of great personal charm, and marked ability as a surgeon. Both of these gifts were at the service of his patients and the hospital, at all times. He rose in stature as a surgeon and as a teacher. During his lifetime he received many honors. The two he cherished most were when you conferred upon him the presidency of the American Association of Genito-Urinary Surgeons, and the



DAVID WALLACE MACKENZIE

presidency of the American Urological Association. He is the only Canadian ever to have achieved these honours.

David Wallace MacKenzie introduced Urology to Canada; he practiced Urology, and he taught Urology. He became known as a surgeon of unsurpassed skill. He was an exacting taskmaster both for himself as well as those he trained. His close friends remember his hobbies. He bred horses; trained horses; and rode horses. His patients remember with gratitude his skill and kindness. All remember his great personal charm. He was a gentleman!

Looking upon these things, the natural sorrow and sense of loss by his family are realized only too keenly. Our sympathy and understanding go out to Mrs. MacKenzie, and their son Dr. David MacKenzie Jr.

Gentlemen, I would ask you to rise in a silent tribute to David Wallace MacKenzie.

WILLIAM CARTER QUINBY

It is difficult to pay unrestrained homage to the memory of a man whom one has cherished and admired as much as I have "Bill" Quinby. His influence and guidance during the formative years of my surgical house-officership, and, later, while I was a resident under him, drew me into the field of Urology. It also set up a standard of professional values which I have sought to achieve ever since. It was, indeed, a fortunate day for me when I was first exposed to his keen mind, his ready wit and his stimulating personality.

William Carter Quinby was born May 26, 1877 at Worcester, Massachusetts. He was the only son of Dr. and Mrs. Hosea Mason Quinby. Following his graduation from Dalzell's School in Worcester, he matriculated at Harvard, where he received his A.B. in 1899 and M.D. degree in 1902. After serving two years as a house officer on the surgical service of the Massachusetts General Hospital, he became associated with a brilliant and talented Boston surgeon, Dr. C. A. ("Allie") Porter. This association was a most fortunate one, because Dr. Porter was an intrepid and imaginative individual whose progressive ideas found ready

WILLIAM CARTER QUINBY

acceptance and application by his younger colleague. In 1910, Dr. Quinby married Marguerite Elizabeth Thayer at Worcester.

In 1912, he left Boston temporarily to take charge of the research in the newly founded Brady Urological Institute at the Johns Hopkins Hospital in Baltimore. Here, under the guidance of Dr. Hugh Hampton Young, he began his researches into experimental and clinical problems dealing with the genito-urinary tract.

In 1916, he was recalled to Boston to become the first urologic surgeon to the Peter Bent Brigham Hospital. This hospital had just been built across from the Harvard Medical School, and offered something new in medical teaching and practice. After 25 years of continuous service, Dr. Quinby became professor emeritus in June 1941. This period of partial retirement was very short-lived. World War II called into service many of the younger men on the Peter Bent Brigham Hospital staff, including Dr. J. Hartwell Harrison, Dr. Quinby's successor, and so he returned to serve as senior urologic surgeon for another four years. During this period, his teaching, research and practice were especially active and fruitful.

In September 1947, he was again recalled by the Brigham Hospital and Harvard Medical School to assume the duties of the Chief and Professor of Surgery, respectively, following the death of Elliott C. Cutler, the Moseley Professor of Surgery. After the selection of Dr. Francis D. Moore as Drs. Cushing and Cutler's successor in July 1948, Dr. Quinby resumed private practice and fulfilled the important role of consulting urologist to the Brigham and Children's Hospital until stricken by illness in June 1951.

In 1923, Dr. Quinby was sent to London in a triple capacity to represent the Brigham Hospital, Harvard University and the American College of Surgeons on the occasion of the 800th anniversary of the founding of St. Bartholomew's Hospital. In the early 1930's he was active in the Harvard Fund Council, and later served as Head of the Doctors' Division of the Greater Boston Community Fund.

Dr. Quinby was a member of the Board of Trustees of the Boston Medical Library, and its Treasurer from 1937 to 1945. For 25 years he served on the Board of Editors of the *Journal of Urology*. In 1929, he was President of the American Association of Genito-Urinary Surgeons and was President of the Boston Surgical Society from 1936 through 1938.

Dr. Quinby, as much as any one individual, served to elevate the specialty of Urology in America to an important place in the general scheme of medical teaching and practice. He was a man of many facets. It was most surprising to find such a thorough and up-to-the-minute knowledge of the basic sciences in a man busily engaged in clinical practice. Due to his ability to read medical literature in several languages, he was always in the forefront of current learning.

Dr. Quinby's many contributions to the physiology of the kidney in his early years still stand as accepted teaching. His clinical contributions are common knowledge to our group.

He was very proud of his membership in this Association, and, during the years

in which he was active in its guidance, he exercised a constant vigilance lest the prize of membership become less valuable and deserving.

During his protracted illness, which ended in his death on December 31, 1952, at the age of 75 years, he exhibited an amazing degree of fortitude and patience.

He is survived by his wife, Marguerite Thayer Quinby and two sons: Dr. John Thayer Quinby of Boston and Dr. William C. Quinby, Jr. of Milton, Massachusetts, and two grandchildren.

May he rest in peace content in the knowledge of a long life devoted to the highest ideals of mankind!!

UTEROVESICAL FISTULA WITH FETAL PARTS PRESENTING IN EXTERNAL URETHRAL MEATUS

MYRON H. NOURSE AND WM. NILES WISHARD, JR.

From the Section of Urology, Methodist Hospital, Indianapolis, Ind.

It was of interest to learn, in review of the literature, that before this same organization and in the same state of Virginia, MacKenzie in 1921 presented a paper on the same subject of uterovesical fistula. Presenting circumstances however were considerably different. As late as 1950 Stening stated, "this type of fistula is so rare that it does not find a place in most manuals of obstetrics and gynecology." We were not in complete agreement with this statement because several case reports were encountered. A rather diligent probe of all publications back to 1876 on the subject of uterovesical fistula fails to reveal a single instance where fetal parts were demonstrable within the bladder and presenting through the urethra as a complication of the pregnancy.

The girl's history was quite informative. A 30 year old white female gravida 4, para 0, presented herself to her family physician August 20, 1951 approximately 6½ months pregnant for prenatal care. Her past history revealed that her first pregnancy was 11 years prior to this time. Her labor was difficult and her child died as a result of toxemia of pregnancy. Her old hospital record said that she leaked urine from her vagina following delivery and returned in 3 months for vaginal repair of a vesicovaginal fistula. Apparently the uterovesical fistula was unrecognized. Since that time, 11 years ago, menses had stopped but cyclic voiding of blood in the urine occurred every month and has persisted to date. She did not need to wear a pad and it was not necessary to interrupt intercourse. Three years later a cesarean section was done for a 6 months dead fetus. She stated that 5 years later she miscarried a 3 months pregnancy through her bladder.

The examination at this time (August 20, 1951) by her family physician showed everything to be essentially within normal limits except that fetal heart tones could not be heard. Blood Kahn was negative. One week later she was admitted to the Methodist Hospital because of lower abdominal cramping interpreted to be uterine contractions. A vaginal examination demonstrated a long, thick cervix with no dilatation. No fetal heart tones could be heard. A torn fetal scalp could be seen coming from the urethra. At this stage we were called to see the patient for the first time (fig. 1). Cystoscopic examination revealed loose pieces of the scalp of the dead fetus with broken pieces of head bones. Visualization at this time was considerably impaired due to the space-occupying foreign body in the bladder. General surgical consultation advised open section which was done immediately. The uterus was closed, a tubal ligation performed but no attempt made to repair the fistula at this time. This was the judgment of the surgeon as he felt the patient's general condition precluded further surgery. Her postoperative course was uneventful and all lochia was discharged through the bladder. An excretory urogram prior to her dismissal on the seventh post-

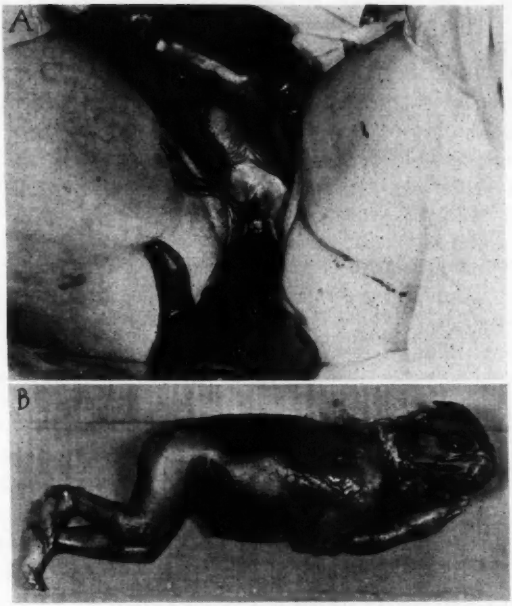


FIG. 1. *A*, fetal scalp emerging from urethra. *B*, dead fetus as it appeared following cesarean section. Note absence of scalp and broken head bones.

operative day showed a normal upper urinary tract. Arrangements were made for her to be re-admitted to the hospital in approximately 3 months' time for repair of her fistula.

Approximately a year later the patient entered the hospital again. Cystoscopic examination showed normal bladder with a fistula opening on the posterior wall in the midline. Repeated cystograms failed to demonstrate communication with the uterus. Upper tract studies were again normal. Urinalysis was negative. On October 1, 1952, through a midline incision, the bladder was opened, the fistulous tract excised and the uterus removed leaving the cervix. The bladder was closed and drained with a urethral catheter. The patient's postoperative course was again without complication and the urethral catheter was removed on the tenth day. She was discharged on the fourteenth day. Follow-up cystoscopy was done one month later and a normal bladder found. There was no urinary difficulty.

COMMENT

From the published data nearly all uterovesical fistulas were secondary to obstetrical procedures or sequelae of radium application, surgical accidents, carcinoma and occasionally tuberculosis. The uterine opening is rarely found in the corpus uteri but nearly all were located in the cervical canal which gave the patient vaginal leakage of urine. There was no vaginal leakage of urine present in our case, therefore placing the opening above the internal os. The conclusions

reached by Sims in 1928 summarize well this subject. I see no reason today to vary his remarks which are as follows:

1) Uterovesical fistulas may be due to trauma in labor with the use of forceps, either by carelessness or incompetence especially in attempt at rotation.

2) They may be caused by uninterrupted prolonged labor with the head on the pubic rami and bladder with strong uterine contractions.

3) According to the histories of the reported cases the complication was not caused by the accoucheur, though he may be reluctant to report in the majority of instances.

4) Practically all fistulas occurred in cases of prolonged labor, contracted pelvis, or a combination of the two, with the bag of water rupturing several hours previous to delivery.

5) The use of pituitary extract may play a part.

6) The incidence is probably more frequent than is observed or reported.

CONCLUSIONS

A case has just been described of a 30 year old white woman 6½ months pregnant, presenting fetal parts in the urinary bladder and through the external urethral meatus.

Several instances of uterovesical fistula have been reported, as evidenced in the bibliography, but to our knowledge ours is the first with this added feature.

1711 N. Capitol Ave., Indianapolis 7, Ind.

REFERENCES

BOND, W. AND ROGERS, G.: Unusual vesico-uterine fistula. Am. J. Obst. & Gynec., **63:** 215–216, 1952.

BRODHEAD, G. L.: Spontaneous closure of large uterovesical fistula. Med. Rec., **98:** 437, 1920.

BRODY, S.: Cervicovesical fistula. Urol. & Cutan. Rev., **55:** 594–597, 1951.

BULLOCH, H.: Uterovesicovaginal fistula. Med. J. Australia, **2:** 709–710, 1922.

BURR, G. C.: Uterovesical fistula. J. Urol., **41:** 906–910, 1939.

CHUTE, A. L.: Suggestion for postoperative care of vesicovaginal fistula. J. Urol., **6:** 77, 1921.

CLEMENTE, D.: Complete, spontaneous uterine rupture during labor; vesico-uterine fistula, cure. Policlinico, **38:** 113–116, 1931.

CONAWAY, W. P.: Vesico-uterovaginal and rectovaginal fistula. J. Med. Soc. New Jersey, **13:** 401, 1916.

COUNSELLER, V. C.: J. Urol., **47:** 711–720, 1942.

COUNSELLER, V. C.: Proc. Staff Meet. Mayo Clinic, **17:** 113–115, 1942.

CURTIS, ARTHUR: Textbook of Gynecology. Philadelphia: W. B. Saunders, 1942, 4th ed.

DOMBIER, M.: Thesis. Paris Chirurg., **40:** 80, 1922.

DOUGLASS, MARION. Juxtacervicovesical fistula. Surg., Gynec. & Obst., **81:** 667–670, 1945.

FORNERO, A.: Surgical therapy of utero-isthmovesical fistula alone and complicated by vesicovaginal fistula; recovery of case. Arch. ital. de urol., **14:** 78–85, 1937.

FRANK, R. T.: Postoperative vesico-uterine fistula. Am. J. Obst. & Gynec., **49:** 776–777, 1945.

GOTTLIEB, J.: Zentralbl. f. Gynäk., **54:** 1090–1092, 1930.

GAUME: Thesis. Paris Chirurg., **13:** 272, 1921.

HAGENBACH, M.: Rupture of uterus with laceration of bladder in connection with personal case. Ztschr. f. Geburshh. u. Gynäk, **89:** 211–228, 1925.

HESS, E.: Atlantic Med. J., **29:** 780–782, 1926.

JONQUAN: Vesico-uterine fistula. Paris Chir., 1909.

KIRCHNER, W. C. G.: Sigmoido-uterine and vesico-uterine fistula as complication of childbirth. Am. J. Obst. & Gynec., **25:** 241–251, 1933.

LAFFONT, A. AND EZES, H.: Uterovesical fistula in unique sense, vesical menstruation. Gynéc. et Obst., **46:** 248–50, 1947.
LEVENANT AND NAGEL: Vesico-uterine fistula. Paris Chir., **75:** 1133–1290, 1916.
LUKE, F. R.: Case of uterovesical fistula treated by hysterostomatocleisis. J. Med. Assoc. South Africa, May 24, 1930.
MACKENZIE, D. W.: Uterovesical and vaginovesical fistula. J. Urol., **6:** 61, 1921.
MACKENZIE, D. W.: Vaginovesical and uterovesical fistula, operative treatment. Canadian Med. Assoc. J., **12:** 95–102, 1922.
MUSSET, R. AND MAZINGARBE, A.: Uterovesical fistula following abdominal cesarean section; 2 cases. Presse méd., **58:** 763–764, 1950.
NICOLIEFF, F.: Treatment of vesico-uterovaginal fistula. Riforma Med., **37:** 199, 1921. (Abstract in J.A.M.A., **76:** 1285, 1921.)
NOECKER, C. B.: Penn. Med. J., **32:** 496, 1929.
PARMENTER, F. J. AND LENTENEGGER, C.: Uterovesical fistula. J. Urol., **10:** 329–334, 1923.
PARRES, A.: Endoscopic therapy of uterovesical fistula. Arch. espän. urol., **5:** 89–95, 1948.
ROLANDO, S.: Uterovesical fistula. Folia Gynaec., **23:** 443–448, 1926.
RUBINS, A.: Brit. Med. J., **1:** 97, 1926.
SCHMITZ, E. F.: Gynecology and obstetrics. Surg. Clinics of North Amer., **5:** 1345, 1925.
SCHOPOHL, F.: Uterovesical fistula due to faulty technique in surgery of urogenital system. Zentrabl. Gynäk., **72:** 1456–60, 1950.
SIMS, G. K.: Spontaneous healing of vesico-uterine fistula following labor; report of case. J.A.M.A., **90:** 759–760, 1928.
STENING, M. J. L.: Vesicocervical fistula. Med. J. Australia, **1:** 12–15, 1950.
SZENDY, A. AND E.: Uterovesical fistula, new operation. Zentralbl. f. Gynäk., **53:** 540–543, 1929.
VERSTRAETÈN, C.: Observation de Fistula Vesico-Uterine Guerie Spontanement. Ann. Soc. de Med. de Gand., **54:** 106, 1876.
VON THOMPSON, H.: Zentralbl. f. Gynäk., **48:** 2566–2568, 1924.
WILLAN, R. J. AND SHAW, A. F. B.: Uterovesical fistula. Brit. J. Surg., **31:** 404–406, 1944.
ZWEIFEL, P.: Monatschr. f. Geburtsh. u. Gynäk., **53:** 3, 1920.

URETHRAL STRICTURE FOLLOWING TRANSURETHRAL RESECTION PREVENTED BY INTERNAL URETHROTOMY: PRELIMINARY REPORT OF EXPERIENCE WITH OTIS URETHROTOME

JOHN L. EMMETT

Section of Urology, Mayo Clinic

AND

JAMES R. WINTERRINGER

Fellow in Urology, Mayo Foundation, Rochester, Minn.

Postoperative urethral stricture continues to be troublesome following transurethral resection, although its frequency of occurrence has diminished sharply since the early days of this operation. Most strictures occur in the pendulous or scrotal portions of the urethra and they usually are tough, rubbery, resilient and respond poorly to dilatation. The most common site of stricture is the penoscrotal junction.

The principal cause of postoperative strictures is now generally agreed to be trauma to the urethra from instruments which are of too large caliber to be admitted easily by the urethra. Other possible etiologic factors include irritation from the urethral catheter, postoperative urethritis, trauma to the urethra at the point of junction of its movable and fixed portions (penoscrotal junction) from the up-and-down and side-to-side motion of the resectoscope (Stratte and Stratte) excessive heat generated in the sheath of the resectoscope, if the electro-urethrotome is used, and a protracted period of operation.

Urethral stricture can be prevented by employing either perineal urethrotomy or a small resectoscope (24F or smaller) if the urethra is too small to accommodate a resectoscope of standard size. Perineal urethrotomy takes advantage of the fact that the bulbous urethra is the portion of the urethra with the greatest caliber. Introduction of the resectoscope through an external urethrotomy boutonnière,* as suggested by Cabot and by Thompson and brought into favor by Nesbit, by-passes the narrower portions of the urethra. Nesbit advised external urethrotomy or use of a small resectoscope in every case in which a 30F caliber steel sound "fails literally to drop into the urethra." In his experience, such a situation is present in approximately 20 per cent of patients who are subjected to transurethral resection.

The caliber of various portions of the so-called normal urethra varies greatly, as does the caliber of the normal urethra from patient to patient. Apropos is the statement of the elder Keyes when, in discussing a paper on internal urethrotomy, he stated, "but what I do feel called upon to condemn is the extensive, indiscriminate cutting of the anterior urethra now commonly indulged in, especially by young surgeons, for any and all possible morbid conditions of the urethra, *simply because the canal is smaller in some parts than it is in others, as the Almighty evidently intended that it should be.*" Anatomists mention the urethral meatus and the membranous urethra (located between the two layers of the triangular

* This procedure was also described in 1902 by Wishard.

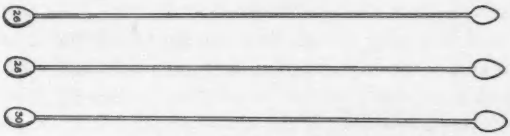


FIG. 1. Otis diagnostic bulbs (bougie à boule).

ligament and surrounded by the external urethral sphincter) as being the two narrowest portions of the urethra, and agree that the bulbous urethra is of the greatest caliber. Of historic interest are the attempts of Otis and of White to correlate the caliber of the urethra with the diameter of the flaccid penis. Some urologists formerly were inclined to the belief that a "normal" urethra should (after meatotomy) easily admit a 30F steel sound and, if such a sound would not pass, that a definite stricture was present. Urologists of the more modern era seem inclined to believe that normal urethras may vary greatly in size and in the absence of a history of stricture, are willing to describe a urethra, which will admit nothing larger than a 24 or 26F sound as a "small normal" urethra.

As mentioned previously, the incidence of stricture following transurethral resection has declined sharply since the early days of transurethral resection. This is the result of such factors as improved surgical technique and instruments, modern chemotherapy and antibiotics and better knowledge of, and respect for the urethra on the part of the surgeon. Nevertheless, a substantial number of postoperative urethral strictures still is seen. It is reasonably certain, also, that, for every patient with such a stricture who presents himself for treatment, there is probably another patient, the caliber of whose stricture is sufficiently large (16 to 18F or larger) so that he voids reasonably well and is satisfied with the result; if such patients should require a further transurethral procedure, however, the stricture would greatly complicate treatment. Causes of most postoperative strictures today, we believe, are two: first, but probably of least importance, is inaccurate preoperative calibration of the urethra; second is the surgeon's hesitation to stop and do external urethrotomy when it is indicated.

Regarding preoperative calibration of the urethra, it is our opinion that minimal urethral narrowing at times may not be appreciated with steel sounds. Too often, in borderline cases, it is difficult to decide whether the sound actually dropped in of its own weight or was helped a little. More accurate calibration of the urethra is possible with the Otis metal bulbs (bougie à boule; fig. 1). With these bulbs it is possible to detect minimal narrowing from the bulb to the urethral meatus, and in addition, to determine the exact location and length of the narrowed portion; this information is almost impossible to obtain accurately with steel sounds. The slightest "jump" of the bulb, either on introduction or withdrawal, indicates a definite point of narrowing. Such a slight jump when using only the 30F bulb is not infrequently encountered and probably would be unnoticed with a sound. We are convinced that this is the type of case in which so often the resectoscope passes easily, yet becomes snug in the urethra during operation.

The hesitation of the surgeon to employ external urethrotomy when it is in-

dicated stems from the fact that he is anxious to get on with the operation; he dislikes to stop and lose part of the time during which the anesthesia can be expected to last. Ten to twenty minutes, or more, may easily be lost with this procedure, depending on such factors as whether or not the perineum already has been prepared; the availability of the necessary instruments; the training and adeptness of the operating personnel, as well as the familiarity of the surgeon with the procedure. These factors, coupled with the slightly lengthened stay in the hospital and the occasional perineal fistula which may persist for two or three weeks, make the surgeon hesitant to use the procedure, especially in borderline cases. For instance, often a 28F sound may pass easily; yet a 30F sound requires a little help. There is no doubt that in the majority of such cases the patients "get by" all right without perineal urethrotomy. Although urethral narrowing develops, it is of insufficient degree in most cases to cause the patient much trouble. As a rule, only patients with fairly marked degrees of narrowing (18F or smaller) return to complain to the surgeon. Because of this the surgeon may be too ready to assume that all will go well and, as a result, strictures continue to occur. Also, small (24F) resectoscopes have not been widely used, especially if the prostate gland is moderately or greatly enlarged, as these instruments definitely increase the difficulty of resection.

It would seem, therefore, that if some simpler, safer and less time-consuming procedure could be devised which would overcome this troublesome problem, it would be a boon to both patient and surgeon. We believe that preliminary internal urethrotomy may be the answer to this problem.

INTERNAL URETHROTOMY PRELIMINARY TO TRANSURETHRAL RESECTION

Internal urethrotomy preliminary to transurethral resection was suggested to the senior author (Emmett) by Dr. Harold McDonald of Atlanta, Georgia who has been using this procedure successfully for several years. Also, White and Berry, of Kingston, Ontario, reported use of this procedure in 1946. Our object here is simply to report our experience with the procedure during the past year. Sufficient time has not elapsed to enable us to make final evaluation but we have been pleased with our results.

Choice of instrument.—We have used the Otis urethrotome (straight model; fig. 2) for several reasons. It was designed principally for the cutting of strictures of large caliber. In its contracted state it is of 16F caliber and can be expanded

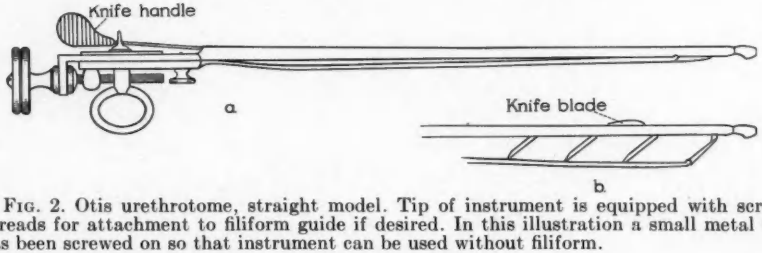


FIG. 2. Otis urethrotome, straight model. Tip of instrument is equipped with screw threads for attachment to filiform guide if desired. In this illustration a small metal tip has been screwed on so that instrument can be used without filiform.

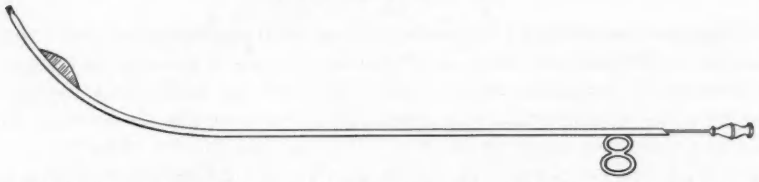


FIG. 3. Maisonneuve urethrotome. Note screw threads on tip of urethrotome for attachment to filiform guide.

(like a Kollmann dilator) so that it can cut as high as 45F. When the straight model is used there is no danger of the instrument's entering the membranous urethra, where it could cut the external sphincter. The curved model would tend to engage the membranous urethra, endangering the external sphincter. Inasmuch as practically all narrow portions which require cutting are in the pendulous or scrotal urethra, the instrument is ideal for our purpose. Further protection against cutting the external sphincter is provided by the fact that the knife blade does not rise out of its slot until it has been withdrawn about 2 cm. from the tip of the instrument. Also, the cutting is done "on withdrawal" of the knife rather than when force is exerted in the opposite direction, as with the Maisonneuve instrument (fig. 3). We have been more pleased with the cold cutting blade than with the high-frequency current as, in our experience, often after internal urethrotomy with the Riba electrotome (Riba and Riba and Sanner), the urethra immediately contracts or goes into spasm, making introduction of instruments most difficult.

Technique.—The technique of the procedure is simple, but it requires accuracy and scrupulous attention to detail. As was mentioned, the first step is careful calibration of the urethra with the Otis bulbs (fig. 1). The urethra is calibrated up to and including 30F. Any narrowing of the meatus or fossa navicularis is corrected by generous meatotomy, in which the floor of the fossa is cut. Following this, calibration is continued. No attempt is made to pass the bulb beyond the bulbous urethra into the membranous urethra. Any evidence of narrowing, including even the slightest jump with the 30F bulb, is regarded as indication for urethrotomy.

The Otis urethrotome is then inserted into the urethra in its closed condition, with the dial and knife slot pointing upward (12 o'clock position of the urethra). The instrument is passed lightly until the tip rests in the bulbous urethra. The object is to make a clean, linear cut in the roof of the urethra to 36F without avulsing or stretching the urethra. To do this, the instrument is expanded slowly and carefully until it is just comfortably snug, following which the knife is withdrawn through the length of the urethra with a brisk, determined motion, so that it will cut cleanly. Explanation of why too much cutting does not result will be made a few lines further on. If this cut was of less than 36F, the blades are closed, the knife is returned to the "home" position and the procedure is repeated until the final cut has been made with the urethrotome blades expanded to 36F, as shown on the calibrated dial. In most cases, this is accomplished in one to three maneuvers. All cuts should be made with the knife at the 12 o'clock position, in

the hope that the cut may be in the septum and that the paired bodies of erectile tissue of the corpora cavernosa penis may be avoided. Care must be taken not to overstretch the urethra by expanding the blades of the urethrotome; otherwise the same trauma would occur as that which occurs with the forcing of too large instruments through the urethra. Following the urethrotomy a 30F sound is passed into the bladder to evaluate the membranous and prostatic urethra. The resectoscope is then passed.

After the resection has been completed, we leave a 26F two-way irrigating Foley bag catheter indwelling for forty-eight to seventy-two hours. This is to allow the incision in the urethra to seal over and partially heal, before the patient voids through it. This procedure, plus administration of antibiotics (penicillin and streptomycin) twenty-four to forty-eight hours before, and for four to six days after operation has, we believe, been important in prevention of febrile reactions. We have been most pleased with the ease of movement of the resectoscope in the urethra throughout the operation following urethrotomy. As every transurethral surgeon well knows, there is nothing that so contributes to the ease of resection as an adequate urethra and a freely moving resectoscope.

To inspect the results, urethroscopy with the panendoscope has been done in several cases after internal urethrotomy. We have noted that the urethra was cut only at the place of narrowing, which usually is at the penoscrotal junction or some point in the penile urethra. The remainder of the urethra is untouched. This is apparently owing to the fact that the knife blade is not particularly sharp and apparently will cut only in areas where there is great resistance. All cuts are made in the roof of the pendulous and scrotal urethra, rather than the floor, to avoid external fistulas. We avoid cutting the membranous urethra for fear of subsequent incontinence, severe bleeding or extravasation.

Regarding healing of the urethrotomy incision, we agree with the opinion of White and Berry that, in the absence of postoperative sounding, the incision probably heals in such a manner that the original caliber of the urethra is restored. Prolonged periods of use of large, indwelling catheters, or postoperative periodic use of large sounds, may result in a urethra of larger caliber.

EXPERIENCE WITH 59 CASES IN WHICH INTERNAL URETHROTOMY WAS PERFORMED

This report concerns 59 cases in which internal urethrotomy was performed with the Otis urethrotome. In 50 cases, the operation was done preliminary to transurethral prostatic resection; in 3, it was done preliminary to transurethral removal of vesical tumors, while in 6, it was done solely for treatment of urethral stricture. These cases represent personal experience of the senior author (Emmett) during the year (May 1, 1952 to May 1, 1953), the time being approximately three weeks short of one year. The 50 cases in which the procedure was done preliminary to transurethral resection represent approximately 20 per cent of the transurethral resections done by the author (Emmett) during the period designated. Nesbit found external perineal urethrotomy required in about the same percentage of cases. For ease of presentation, we are combining in one group the

50 cases in which internal urethrotomy was done to facilitate transurethral prostatic resection and the 3 cases in which it was done for transurethral removal of vesical tumors. The 6 cases in which the operation was done only for treatment of bona fide urethral stricture comprise a second group.

FIFTY-THREE CASES IN WHICH INTERNAL URETHROTOMY WAS DONE PRELIMINARY TO A TRANSURETHRAL SURGICAL PROCEDURE

As has been mentioned in this paper, there is no agreement as to the distinction between a bona fide stricture and a small normal urethra. For clarity we have made the following arbitrary definitions: If the caliber of the urethra is 26F or larger, and if there is no history of previous disease or trauma which might have caused stricture, we have classified the urethra as a small normal one. On the other hand, if the caliber of the urethra is 24F or smaller, or if there is a definite history of previous urethritis or trauma which could have caused stricture, either or both, we have classified the urethra as one in which there is a stricture.

On the above basis, of the 53 urethras, 37 were classified as small normal and 16 were said to be strictured. Of the 37 small normal urethras, preoperative calibration revealed the following: 26F, in 7 instances; 28F, in 11 instances; 30F in 19 instances. By 30F we mean that there was a definite jump or "hang" when the 30F bulbs were passed. Larger bulbs were not used in calibration. The site of narrowing in the 37 cases was as follows: penoscrotal junction in 21 cases and pendulous urethra in 16 cases.

Of the 16 urethras which were classified as strictured, preoperative calibration revealed the following: 16F in 2 instances; 22F in 3 instances; 24F in 7 instances and 26F in 4 instances. The site of stricture was as follows: penoscrotal junction in 8 cases; pendulous urethra in 7 cases, and the site was not noted in 1 case. The etiology of these 16 strictures was as follows: previous urethral instrumentation in 10 cases; urethritis in 2 cases, and no history in 4 cases.

Of the entire 53 cases, in 47 the urethra was cut to 35 or 36F while, in the other 6, the cut was to varying calibers from 32 to 34 F. These latter cases were gathered during our earlier experience. As we have said, it is now our standard practice to cut the urethra to approximately 36F, because we have found that anything less than this may result in the resectoscope's becoming tight in the urethra during resection.

Four of the 53 cases require some individual explanation. In 2 cases, a 30F bulb seemed to pass freely, yet the resectoscope became a little snug after the resection had progressed for a few minutes; therefore, the resectoscope was withdrawn and urethrotomy was done, cutting to 36F. In 1 of the 2 cases, the resectoscope moved freely during the remainder of the operation. In the other, it again became slightly snug near the end of the operation. We feel that probably we were a little inaccurate in calibration in these cases. The other 2 cases of the 4 which require explanation were as follows: In 1, the urethra was cut before operation (at the penoscrotal junction) from 26 to 35F, following which a 30F bulb passed easily and the resectoscope passed easily. In spite of this, the resectoscope became a little snug toward the end of the operation but not enough to require further

urethrotomy. In the other case, the urethra was cut from 24 to 34F, in spite of which the resectoscope became so snug in the course of the operation that it was removed and the urethra was cut to 36F. Following this, the resectoscope moved freely throughout the entire operation.

We have encountered no troublesome bleeding from urethrotomy. During resection the pressure from the sheath of the resectosope apparently has been sufficient to control bleeding, as has the presence of the 26F indwelling bag catheter, postoperatively. In only 1 case did we find it necessary to put a compression bandage on the penis to make pressure against the catheter and in this case the bleeding was not excessive. We have not observed pain or discomfort as a result of the procedure.

We have noted no increase in the incidence or severity of postoperative febrile reactions. This no doubt is partially attributable to our routine use of antibiotics, which was previously described. Another factor may be the two-way irrigating Foley bag indwelling catheter, our use of which also has been described; it may minimize the possibility of absorption into the general circulation during voiding.

Patients usually are allowed to leave Rochester on the twelfth to fourteenth postoperative day. In each case, two days before their departure, we have passed a 26 or 28F sound and, in every case, the sound has passed easily and freely. A 30F sound has not been used, to avoid unnecessary discomfort to the patient.

Late results and complications.—Inasmuch as all of the patients concerned in this report have been operated on in the course of the year beginning May 1, 1952, long-term follow-up has not been possible. In our experience, however, most postoperative strictures become apparent within 6 months; hence, this preliminary report may have more significance than would appear from a cursory survey. Patients who live near Rochester have been asked to return periodically for urethral calibration. Letters have been written to the remaining patients and their physicians, requesting that calibration be carried out at home. We soon learned that patients who are having no trouble voiding are not anxious to submit to the discomfort, even if only minimal, of having a sound passed through the urethra. For this reason our follow-up response has not been as prompt as we would like it to be. In spite of this, we have been able to secure results of follow-up study on 24 of the 53 patients; 10 returned to the clinic, while 14 were examined by their home physicians. Of these 24 cases, 11 represent a follow-up period of six to ten months; 7 represent a follow-up period of three to six months; 3 represent a follow-up period of two to three months, while in 3, the follow-up period was less than two months.

Before we give the results of this study, however, we wish to report that none of the 53 patients has written complaining of any difficulty with the urinary stream. Metal Van Buren sounds, caliber 26 or 28F, have been passed through the urethras of all 24 who have been followed and, in only 1, was any evidence of urethral narrowing found. Larger sounds were not passed because of discomfort to unanesthetized patients. We have employed sounds rather than diagnostic bulbs in order that the prostatic urethra and vesical neck could be calibrated at the same procedure. In the cases in which we ourselves have been able to make the re-examination, we have been impressed with the adequacy of the urethra.

In the 1 case in which re-examination gave evidence of some narrowing of the urethra, the patient had been treated transurethrally many times for a vesical tumor. Symptoms of prostatic obstruction finally demanded transurethral resection. Previous instrumentation had resulted in a stricture of about caliber 24F at the penoscrotal junction. It was cut to 36F to admit the resectoscope. Re-examination in six months revealed some tightness in the penoscrotal junction but it was not accurately calibrated. Re-examination in ten months showed the caliber of the penoscrotal junction to be approximately 20F.

We have been especially interested to know whether any late manifestations of fever or sepsis are likely to occur as a result of this procedure. As far as we can determine, only 1 patient has had a delayed febrile reaction. This was a man who had an extensive infiltrating carcinoma of the bladder for which, on many occasions, he had received transurethral fulguration and radon seeds had been implanted. As a result of this instrumentation, a dense stricture of approximately caliber 16F had developed at the penoscrotal junction. For the purpose of inserting an instrument for fulguration of a recurrent tumor, internal urethrotomy was done. The catheter, however, was left in place for only two days. This probably was not sufficiently long because, after he had returned home he was ill in a hospital for two to three weeks with recurring fever. There were no localizing signs, however, and the fever gradually subsided. We now would treat such a patient in our routine manner, using antibiotics and an indwelling catheter. These measures, we believe, would have prevented the complication.

Although we have had no serious complications in our past year's experience with internal urethrotomy, we feel certain that sooner or later we will encounter some troublesome complications such as bleeding, infection, or even sepsis. Nevertheless, we also are of the opinion that, with careful technique and attention to details, complications should be minimal and should not seriously detract from the great advantages of the procedure.

SIX CASES IN WHICH INTERNAL URETHROTOMY WAS DONE SOLELY FOR URETHRAL STRICTURE

In 6 cases, internal urethrotomy was done for the sole purpose of treating advanced, intractable stricture of small caliber, attempts at dilatation of which had failed. In each of 3 of these cases, more than 1 stricture was present; 1 stricture was in the bulbous urethra, while the other was either at, or just distal to, the penoscrotal junction. In 2 of these 3 cases, the strictures were results of previous gonorrheal urethritis, while in the third case they had been caused by injury. In all 3 cases, sufficient dilatation was achieved with filiforms, followed by flexible Phillips' catheters or LeFort sounds, to allow the urethrotome (16F) to be passed. Successive cuts then were made through the strictures until a caliber of 36F had been reached.

In the 3 cases in which strictures were only single, 2 were situated at the penoscrotal junction, while the third was in the pendulous urethra. One was the result of old gonorrheal urethritis while the other 2 were the result of previous urethral instrumentation.

The immediate result in all cases was excellent. All operations were performed

under anesthesia, in the hospital, and large (26F) Foley bag catheters were left indwelling. Patients were allowed to leave the hospital at the end of forty-eight or seventy-two hours, with the catheter in place and a clamp attached. Each patient was instructed to release the clamp when voiding was necessary. Patients were requested to wear the catheter for at least two weeks, and longer if tolerated, to minimize further scarring and reduction in caliber of the stricture. Doss has suggested that six weeks should be the minimal time.

We have follow-up data on only 2 of these 6 patients. One, who had the most severe stricture of all, was operated on five months ago. The patient's home urologist has stated that a 25F sound now passes easily, although it had not been possible to pass a sound of that size in this case for many years. Previously, sounding had given no relief. The other patient of the 2 had an old gonorrheal stricture of the penile urethra. He also has been followed for five months. His home physician has stated that a 28F sound passes easily.

PAST HISTORY OF INTERNAL URETHROTOMY

Although the results which have been outlined make a favorable case for internal urethrotomy, the procedure should not be accepted without examination of its past record. About all that most present-day urologists know of internal urethrotomy is that it lost favor about the turn of the century.

Maisonneuve devised the urethrotome which bears his name about 1850. Otis, then clinical professor of venereal diseases at the College of Physicians and Surgeons in New York, announced his instrument before the New York Journal Association in 1871, and the report was published in 1872. Both instruments were devised for treatment of advanced urethral stricture, which was a common and troublesome problem in that era. The Maisonneuve instrument (fig. 3) was designed for cutting strictures of small caliber and, although blades of different sizes could be obtained for the instrument, it was not designed to cut the urethra to as large caliber as the Otis instrument, which will cut to 45F. As a matter of fact, as mentioned previously, Otis's only claim that his instrument was superior to the Maisonneuve instrument was that it could be used to cut strictures of "large caliber." Over the years, extensive trial was made of internal urethrotomy and it was much in vogue until about the turn of the century, (Harrison) when its use became considerably curtailed. The reason for its curtailment seems to have been an excessive mortality rate and a substantial incidence of complications, (Harrison, Huddy) the more common of which were sepsis, hemorrhage, extravasation and penile curvature (chordee).

Mortality rate of internal urethrotomy.—In trying to evaluate, from the literature, the risk of the procedure, it is important to appreciate the era in which the operations were carried out. Most of the large series of operations were done in the days when not much was known about sepsis and antisepsis. For that matter, most of the modern series of operations reported were done before the era of modern chemotherapy and antibiotics. Surgical technique has improved greatly over the years and there is no comparison between the risk of internal urethrotomy done forty years ago as an office procedure with that done now in a hospital,

with the benefit of anesthesia and of the other measures mentioned herein. It must be remembered also that in the old days many of the chronic, long-standing strictures were associated with chronic urinary infection, advanced renal disease and chronic perineal infection, abscess and fistula. They constituted a hazard to life, even in the absence of instrumentation of any kind.

With the above explanation, a sampling of the literature in regard to mortality and morbidity should be interesting and instructive. Giraud (1936) reviewed the mortality rates before the turn of the century by citing series of cases from both Tillaux and Maisonneuve. Tillaux reported 47 cases, with 13 deaths; Maisonneuve reported one series of 36 cases, with 2 deaths, and another series of 66 cases, with 3 deaths. Giraud then made evident improvement in mortality in the modern era by quoting Minet, who reported a series of 200 cases, with no deaths. In 1909, Cabot stated that the mortality rate from internal urethrotomy was approximately 1.5 per cent, but he added that under "modern" conditions it should not be more than 0.5 per cent. Lydston quoted Otis as stating that he had performed the operation in 900 cases with no deaths. In Winsbury-White's *Textbook of Genito-Urinary Surgery* (1948 edition), the statement (Loughnane) is made that the mortality of internal urethrotomy is 1.5 per cent. In the 1936 edition of Thomson-Walker's book *Surgical Diseases and Injuries of the Genito-Urinary Organs*, the following statement is made regarding the risk of internal urethrotomy: "In most cases where death has followed the operation it has resulted from an exacerbation of pre-existing disease and not from any new factor introduced by the operation itself. During thirteen years (1895 to 1908) 1,018 patients suffering from stricture were treated by internal urethrotomy at St. Peter's Hospital, and 8 patients died, a mortality of 0.78 per cent. Watson and Cunningham united several series of cases recorded in the literature and found 53 deaths in 4,686 cases, a mortality of 1.1 per cent. The causes of death were exacerbation of old-standing pyelonephritis (50 per cent), anuria and uremia, septicemia and hemorrhage." Riba (1939) reported 150 cases in which operation was done with his electro-urethrotome, with no mortality. Davis and Lee (1948) reported a series of 45 cases, in most of which, apparently, operation was done with the Maisonneuve urethrotome, with 1 postoperative death.

Results of internal urethrotomy for stricture.—Will internal urethrotomy "cure" the urethral stricture or is repeated urethral dilatation necessary afterward? Here again many different opinions are obtainable from the literature. Lydston (1893) had this to say: "Too vigorous postoperative sounding contributes to hemorrhage, urethritis and curvature of the penis. Best results follow infrequent dilatation, beginning the third postoperative day and every three days for one week, then every four or five days . . . . I do not at the present time consider it necessary, as a rule, to pass sounds after the operative wound has healed, for I have acquired a great faith in the permanency of my results." Cabot (1909) recommended postoperative sounding followed by irrigation of the urethra every other day for two weeks, then "at less frequent intervals as with any other stricture." Koll (1918) expressed the belief that postoperative dilatation with sounds was necessary and stated that it required as much and as long sounding as if dilatation were done

originally. Davis and Lee (1948) stated, "Recurrence of the obstructive symptoms and a return to the 'status quo' during a few weeks has been the rule, rather than the exception." Doss has advocated the patient's wearing a 24 or 26F, indwelling bag catheter for four to six weeks following urethrotomy, to prevent recontraction, and he has concluded that it has been very effective.

In reviewing these opinions one wonders whether the permanency of results is not, to some degree at least, dependent on the caliber to which the stricture has been cut. For instance, in Davis and Lee's series of cases they treated strictures of the "deep" (bulbomembranous) urethra as well as those of the pendulous and scrotal urethra. They, therefore, used the curved Maisonneuve urethrotome which is of 8F caliber. The maximal depth to which the blade of this instrument would cut was 6 mm., which roughly means that the urethra was cut to a caliber of only 25F. They further stated, "After passage and removal of the guide, the urethra is dilated with sounds or with filiform and followers. Even with tight strictures, there is seldom any difficulty in carrying the dilatation up to 26 or 28F."

It is difficult to find any definite statements or advice in the literature as to how "wide" a stricture should be cut. Lydston stated, "The determination of the size to which the urethra should be properly enlarged involves some nicety of judgment." Evidence, however, that he no doubt cut most strictures to a caliber of at least 32 to 35F appears in the statement, "In fact, it will often be found impracticable to maintain a caliber of more than 32 to 35F, even where the urethra has been incised and stretched to the fullest capacity attainable by the Otis dilating urethrotome (45F)." The elder Keyes (1880) stated that the stricture "must be cut so as to be considerably larger than the normal urethra at that point; and that to insure the best results, a single cut should be made—a cut, if possible, *to pass beyond all diseased tissues and into the healthy tissue*."

PRESENT EXPERIENCE, IN LIGHT OF PAST HISTORY AND THE PROBABLE FUTURE

Our experience with the small group of cases presented herein lends weight to the dictum that urethrotomy must be wide. Preliminary to transurethral resection we have found it necessary to cut the urethra to 36F to be sure that the resectoscope will move easily throughout the operation. Because of this, we also have cut to 36F the few bona fide strictures with which we have had to deal without encountering any serious complications. Further experience may well demonstrate that satisfactory permanent results are dependent on sufficiently wide incision of the stricture.

Indications for internal urethrotomy for urethral stricture.—Over the years, experience with internal urethrotomy has resulted in a more or less generally accepted set of rules and indications for internal urethrotomy. These are evident in the writings of pioneers in urology, such as Gross, Keyes, Keyes and McLellan, Kidd, Young and Davis, Cabot, Caulk, Bartels, Pedersen and many others. The situation is admirably crystallized in the statement of Keyes, which has been memorized by many medical students, "Never cut if you can dilate." If the physician adheres to this advice, he will cut very few strictures of the bulbo-

membranous urethra because nearly all will respond to adequate periodic dilatation. On the other hand, he will cut many strictures of the pendulous and scrotal urethra because, inherently, strictures in this location are tough, resilient and either cannot be dilated or will not remain dilated. (Hyams) That this continues to reflect modern opinion is seen from the statement by McIntyre and Nesbit (1934): "Urethrotomy in one or another form, supplemented by repeated dilatation, will probably continue to offer the best result in stricture of the pendulous urethra." Terms which have been used in the literature to describe the types of strictures (especially of the pendulous and scrotal urethra) which should be subjected to urethrotomy include the following: "resilient," "rubbery," "dense," "unyielding," "highly elastic," "cicatricial," "old, gristly and intractable," "resistant and irritable" and "indisposed to yield to dilatation." Adherence to the advice of Keyes will automatically protect against the rather serious complications that have been found to occur not infrequently when internal urethrotomy is performed in the "deep" bulbomembranous urethra. Whether or not further experience in this modern era of better technique, chemotherapy, antibiotics and indwelling urethral catheters will modify these indications remains to be seen. We have suggested one additional indication for urethrotomy, namely the need to enlarge a small normal urethra preliminary to passage of a resectoscope in order to perform transurethral resection. Also, we should not neglect to mention that years ago both Cabot and Joly suggested the use of internal urethrotomy to increase the caliber of the urethra for the successful performance of litholapaxy.

SUMMARY AND COMMENT

There are now two important indications for internal urethrotomy: 1) the presence of resilient strictures, especially those of the pendulous and scrotal urethra, which will not permit adequate dilatation, and 2) the need to enlarge the pendulous and scrotal urethra (either a "small normal" urethra or definite stricture) to permit the passage of large operating instruments, such as the resectoscope and the lithotrite, without the production of subsequent postoperative stricture. We believe it possible that internal urethrotomy may gradually replace perineal urethrotomy when transurethral resection must be performed through a urethra of small caliber. Whether or not this prediction is sustained will depend largely on care and scrupulous adherence to details by the surgeon, to prevent untoward complications. It must be remembered that, by internal urethrotomy, an opening may be made into large venous channels such as those of erectile tissue, permitting even more ready access of foreign material and infection into the general circulation than does the prostatic capsule during transurethral resection. Because of this, the same precautions shown to be effective in transurethral resection should be adhered to, namely administration of antibiotics twenty-four to forty-eight hours before, and for several days after, operation as well as adequate care devoted to drainage by indwelling urethral catheter for at least four days. Such drainage permits the urethral incision to seal over, and prevents the patient's voiding into the general circulation via the cavernous tissue or an unhealed urethra. If such precautions are scrupulously observed, it

is our opinion that the procedure will prove to be of such minimal risk that it may be employed before transurethral resection whenever desirable. Whether or not further experience, with benefit of modern technique and suitable precautions, will enlarge the indications for the procedure in the presence of urethral stricture remains to be seen.

REFERENCES

BARTELS, LEO: A plea for less operative interference in treatment of organic stricture of the urethra. J. Missouri M. A., **14:** 479–483, 1917.

CABOT, HUGH: Chancroid, gonorrhea and its complications; stricture of the urethra. Reprinted from American Practice of Surgery. (Edited by J. D. Bryant and A. H. Buck.) New York: William Wood & Co., 1909, vol. 6, pp. 700–812.

CAULK, J. R.: Discussion. J. Missouri M. A., **14:** 484, 1917.

DAVIS, EDWIN AND LEE, L. W.: Lasting results following internal urethrotomy for urethral stricture. J. Urol., **59:** 935–938, 1948.

DOSS, A. K.: Personal communication to the authors.

GIRAUD, D.: Du traitement des rétrécissements de l'urètre par la dilatation permanente progressive. Ses avantages sur l'urétrotomie interne. J. d'urol., **42:** 415–431, 1936.

GROSS, S. D.: A Practical Treatise on the Diseases and Injuries of the Urinary Bladder, the Prostate Gland and the Urethra. Philadelphia: Blanchard and Lea, 1851, pp. 645–649.

HARRISON, REGINALD: The Urethrotomies and Kidney Capsulotomy in Diseases and Injuries of the Urinary Organs. London: John Bale, Sons & Danielson, Ltd., 1906, 96 pp.

HUDDY, G. P. B.: Some considerations of the operation of internal urethrotomy and the end-results thereof. Brit. J. Surg., **13:** 458–465, 1926.

HYAMS, J. A.: Diagnosis and treatment of stricture of male urethra. Am. J. Surg., **36:** 189–196, 1937.

JOLY, J. S.: Stone and Calculous Disease of the Urinary Organs. St. Louis: C. V. Mosby Co., 1929, pp. 468–469.

KEYES, E. L.: The Venereal Diseases, Including Stricture of the Male Urethra. New York: William Wood & Co., 1880, pp. 290–310.

KEYES, E. L., JR.: Diseases of the Genito-urinary Organs Considered From a Medical and Surgical Standpoint, Including a Description of Gonorrhea in the Female and Conditions Peculiar to the Female Urinary Organs. New York: D. Appleton and Company, 1911, 975 pp.

KEYES, E. L. AND MCLELLAN, ALLISTER: Stricture of the Urethra. In Cabot, Hugh: Modern Urology: In Original Contributions by American Authors. Philadelphia: Lea & Febiger, 1936, vol. 1, pp. 367–395.

KIDD, F. S.: Urinary Surgery; a Review. London: Longmans, Green & Co., 1910, 429 pp.

KOLL, I. S.: Diseases of the Male Urethra, Including Impotence and Sterility. Philadelphia: W. B. Saunders Co., 1918, pp. 78–101.

LOUGHNANE, F. McG.: Inflammatory Urethral Stricture. In Winsbury-White, H. P.: Textbook of Genito-urinary Surgery. Baltimore: The Williams & Wilkins Co., 1948, pp. 638–655.

LYDSTON, G. F.: Stricture of the Urethra. Chicago: The W. T. Keener Company, 1893, 334 pp.

MAISONNEUVE: Quoted by Attwater, H. L.: The history of urethral stricture. Brit. J. Urol., **15:** 39–51, 1943.

MCDONALD, H. P.: Care of patient following prostatic resection. South M. J., **38:** 260–263 1945; also, personal communication to the authors.

MCINTYRE, C. H. AND NESBIT, R. M.: Treatment of filiform urethral stricture by method of continuous dilatation. Urol. & Cutan. Rev., **38:** 98–99, 1934.

NESBIT, R. M.: The advantages of perineal urethrotomy in prostatic resection. South. Surg., **7:** 501–504, 1938.

NESBIT, R. M.: Transurethral Prostatectomy. Springfield, Ill.: Charles C. Thomas, 1943, 192 pp.

OTIS, F. N.: Remarks on strictures of the urethra of extreme calibre, with cases, and a description of new instruments for their treatment. New York M. J., **15:** 152–174, 1872.

PEDERSEN, V. C.: A Text-book of Urology in Men, Women and Children, Including Urinary and Sexual Infections, Urethroscopy and Cystoscopy. Philadelphia: Lea & Febiger, 1919, pp. 362–363; 390–395.

RIBA, L. W.: Electro-urethrotomy in the treatment of urethral stricture. J.A.M.A., **106:** 1971–1975, 1936.

RIBA, L. W.: Treatment of small caliber strictures of anterior urethra by electro-urethrotomy. J. Urol., **42:** 906–907, 1939.

RIBA, L. W. AND SANNER, J. E.: Treatment of urethral strictures of small caliber by a new method: Preliminary report. J. Urol., **30:** 361–366, 1933.

STRATTE, J. J. AND STRATTE, JOHN: Strictures following transurethral resection; comments on the indication for the operation. Am. J. Surg., n.s. **73:** 503–509, 1947.

THOMPSON, G. J.: Perineal prostatic resection. Proc. Staff Meet., Mayo Clin., **12:** 360–362, 1937.

THOMSON-WALKER, J. W.: Surgical Diseases and Injuries of the Genito-urinary Organs. Baltimore: William Wood & Co., 1936, 974 pp.

WATSON, F. S. AND CUNNINGHAM, J. H., JR.: Quoted by Thomson-Walker.

WHITE, E. P. AND BERRY, N. E.: Stricture formation following transurethral resection; its prevention and treatment. Urol. & Cutan. Rev., **50:** 662–664, 1946.

WHITE, J. W.: The treatment of stricture of the male urethra. Univ. M. Mag., **3:** 291–312, 1891.

WINSBURY-WHITE, H. P.: Textbook of Genito-urinary Surgery. Baltimore: The Williams & Wilkins Co., 1948, 1046 pp.

WISHARD, W. N.: The use of the cautery on the prostate through a perineal opening. New method with presentation of instrument and report of cases. J. Cutan. Dis., **20:** 245–252, 1902.

YOUNG, H. H. AND DAVIS, D. M.: Young's Practice of Urology; Based on a Study of 12,500 Cases. Philadelphia: W. B. Saunders Co., 1926, vol. 2, pp. 566–569.

DISCUSSION

Dr. David M. Davis (Philadelphia, Pa.): I would like to confirm everything that Dr. Emmett has said. I only wish that it had occurred to me to publish an article about urethrotomy preceding transurethral resection myself.

I cannot even recall the first time I used this method, but it has been well over ten years ago. I do not know how many times I have used it during that period, but it has been a great many times, always with excellent results, and never with any serious complications.

Recently there was a case of some interest in that connection. A very bad, old gonorrheal stricture had been treated by dilatation for years, always with a heavy infection. After a while the patient consented to a thorough investigation, and it appeared that he had not only stricture but a contracture of the vesical orifice, and two rather large diverticula of the bladder. Hoping to help him, we did perform internal urethrotomy, size 32, and resected the contracture of the vesical orifice.

Unfortunately, the results of this were poor because of the residual infection in the retentive diverticula, so it was necessary to continue dilatation of the urethra every two weeks over a long period of time.

He finally persuaded himself to return to the hospital where he underwent diverticulectomy. This time the urethra was again opened to size 32 by internal urethrotomy and I trust that the infection will now subside.

Dr. Donald Charnock (Los Angeles, Calif.): I recently had the privilege of dilating one of Dr. Emmett's cases. As Dr. Emmett has so graphically described to you, this gentleman spent a good deal of time trying to argue me out of the dilatation. I finally said to him, "Look, Dr. Emmett wrote you that he wanted your urethra dilated." He gracefully submitted. The man had a very excellent urinary stream. The urine was entirely negative.

Dr. Emmett: After Dr. Davis's question, he turned around and wondered if they were still making those urethrotomes, or had started making them again. We ordered a bunch from Germany, and they are supposed to be on the market.

RESULTS OBTAINED BY ENDOCRINE CONTROL THERAPY FOLLOWED BY RADICAL PERINEAL PROSTATECTOMY IN TWENTY-FIVE SELECTED CASES OF ADVANCED CARCINOMA OF PROSTATE

W. W. SCOTT

From the Department of Surgery, Division of Urology, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.

It was to be expected that the marked regression of the carcinomatous prostate which so frequently resulted from endocrine control therapy would suggest to a number of observers a broadened field of usefulness for the perineal prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate. Vallett in 1944 seems to have been the first to use this combined therapy on a case of this sort but unfortunately the patient died too soon after surgery to permit any conclusions as to its efficacy. Later in the same year Parlow and then Colston recommended its use in selected cases. In December of that year Scott and Benjamin reported 2 cases which had recently been treated in this manner. In 1947, Colston and Brendler reported one death within a year in 7 cases that had been followed 2 years after surgery. Parlow and Scott in 1949 reported their results in a series of 14 cases treated by this combined therapy. One year later Scott and Parlow reported that 22 cases had been treated by this method in their clinic and presented a detailed report on the first 13 cases, all of which were living and apparently well after the institution of therapy. Scott in 1953 presented a detailed report on 21 selected cases of advanced carcinoma of the prostate that had been treated by this method and which had been followed three years or more after treatment was started.

Inasmuch as any attempt to evaluate the efficacy of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland is necessarily influenced by the types of case included in such a study, it might be helpful if our determining selective factors were presented and discussed at this time. Obviously those patients, in whom, because of recent origin or latency of growth, the carcinoma, when first discovered, is so situated as to permit a reasonable chance for its complete removal by radical surgery, should not be included in this group. All patients with proven metastases when first seen, regardless of their response to hormone therapy, are not suitable candidates for the follow-up radical surgery. Radical surgery offers practically no hope of cure to the patients without metastases in whom the local growth is a little too extensive to permit its complete removal when first seen and who fail to respond to endocrine therapy. Where the local growth has advanced to such an extent as to result in the formation of a well-defined, intervesicular plateau when the patient is first seen, it is reasonable to assume that lymphatic and perineural extension beyond the palpable area may have occurred even though the presence of metastases cannot be proven. In such cases, regardless of a remarkable local response, it would seem that while a follow-up radical perineal prostatectomy

This investigation was supported by funds from the Dr. Henry C. Buswell Memorial.

might increase the patient's life expectancy and freedom from distressing urinary symptoms, it should still be considered of questionable value. In the presence of nodular intravesical extension beyond the bladder neck when the patient is first seen, the combined therapy seems to be contra-indicated. However when the aforementioned conditions have been excluded there still remains a very encouraging number of cases with carcinoma of the prostate from which the patients to be treated by the combined therapy can be selected.

These are the patients in the group of advanced carcinoma of the prostate without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is examined. It is for the patients in this group, providing their response to hormone therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure, or failing in this will at least prolong the patient's life and freedom from distressing symptoms. But even some of these patients have to be excluded because advanced age or their general physical condition seem to contra-indicate radical surgery.

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition. Because of their limited life expectancy and because carcinoma of the prostate is often a very slow process in patients who are 80 or more years of age, we have not used the combined therapy in any instance where the patient was that old when first seen. We have learned that as a result of careful preoperative and postoperative care, proper supportive measures during operation and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while sometimes requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate. At least three of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case. As a rule the operative risk due to the presence of general physical disability is little if any greater than that of the other open operations upon the prostate for the correction of prostatic obstruction.

Up to the present time in the urological clinic of the Strong Memorial Hospital, we have treated 31 patients by this combined therapy, 25 of whom have been followed 36 months or more since treatment was instituted. The remaining 6 patients have not been under treatment long enough to warrant an attempt to evaluate the efficacy of the therapy upon them.

Since 21 of the 25 cases that have been followed 3 years or more have been presented in detail in a very recent publication, it might be more profitable at this time to present and discuss in detail the 5 cases in our series in which death was due to local recurrence or metastasis. In all the patients treated by this method the clinical, serological and radiographic studies were negative for the presence of metastasis. Furthermore all blood studies and renal function tests were within normal limits at the time of operation.

CASE REPORTS

Case 1. C. D., S.M.H., 211137, aged 72 when first examined on November 1, 1943, gave a history of gradual diminution in size and force of his urinary stream, increasing frequency and terminal dribbling of 6 months' duration. There had been no loss of weight.

The findings on physical examination were normal for a man his age except for the prostate which was moderately enlarged in all dimensions; its median furrow and notch were shallow and its surface was moderately smooth but very hard. It was fixed in position and extension beyond the base to the region of the seminal vesicles for a short distance had occurred on each side (fig. 1, *A*). His residual urine was 15 cc and a punch biopsy study revealed adenocarcinoma of the prostate.

Following a bilateral orchiectomy, performed on November 22, 1943, regression which was slow and not marked except in the anteroposterior diameter of the gland, reached its maximum point on November 14, 1944 when a follow-up radical perineal prostatectomy was performed. At that time there still remained some induration extending for a short distance towards the seminal vesicle in each side (fig. 1, *B*).

Studies of sections from the surgical specimen showed a scattered collection of large epithelial cells with hyperchromic nuclei and abundant pale-staining cytoplasm. Some of the cells were arranged in acinar fashion, but for the most part, they appeared as solid cords invading the dense connective tissue and smooth muscle. Cancer cells were found in the fascial tissue surrounding the seminal vesicles. Sections of nerves showed tumor cells within their sheaths.

The patient's convalescence was satisfactory and when he was discharged from the hospital 23 days after operation he was voiding satisfactorily and his control was perfect.

Because of his poor response to bilateral orchiectomy the patient was not placed on our routine postoperative course of estrogen therapy until a recurrent nodule was discovered on rectal examination 56 months after prostatectomy (fig. 1, *C*). He was immediately started on stilbestrol therapy which was later supplemented by deep x-ray and local radium treatments. He died of carcinomatosis on May 26, 1950.

This case failed, in at least one respect, to meet our criteria for treatment by this combined therapy. The growth, which was well beyond the confines of the prostate in the region of the seminal vesicles when the patient was first seen,

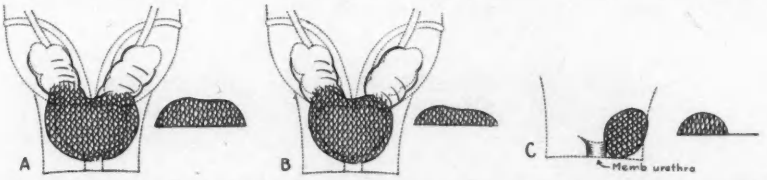


FIG. 1. *A*, prostate before castration November 11, 1943. *B*, only slight regression evident at time of radical perineal prostatectomy November 11, 1944. *C*, location and size of recurrence when first discovered on June 6, 1949.

responded but slightly to control therapy and therefore it is doubtful if a reasonable chance for its complete extirpation was present at the time of radical surgery. Inasmuch as during most of the 82 months that the patient lived following the institution of therapy he was quite comfortable and without urinary symptoms, it would seem that he derived some benefit from the treatment. We believe that we are now able to evaluate the surgical possibilities in cases of this sort much more accurately than at the time this patient was treated.

Case 2. O. J., S.M.H., 237491, aged 61 when first seen on September 17, 1943 complained of gradually increasing frequency, dysuria and dribbling of 3 years' duration.

He appeared to be in good physical condition but on rectal examination a prostate that was very hard and enlarged in all dimensions was found. There was extension of third degree induration beyond the base to the region of both seminal vesicles with beginning intervesicular plateau formation (fig. 2, *A*).

Stilbestrol therapy, 5 mg. a day, gave considerable relief of urinary symptoms but regression was slow so a bilateral orchiectomy was performed on April 5, 1945 and the estrogen therapy was continued. Within 4 months the involved area had regressed and softened markedly. It was firm but movable in spite of definite adhesions along its lateral margins (fig. 2,*B*). The radical perineal prostatectomy was performed on September 9, 1945.

On examination of the gross specimen an area of nodular hardness was found in the region of one seminal vesicle but there was no note that sections were taken from it. The tumor was of a diffuse infiltrating type. In some areas the connective tissue was studded with small acini, nests and cords of tumor cells. Many of the nests contained only 2–3 cells. Studies of sections from the periphery of the surgical specimen in a few instances showed cells in acinar form invading the nerve trunks.

The patient's convalescence was uneventful except that he had almost complete incontinence for a period of 2 weeks following the removal of his catheter. When discharged 28 days after operation his control was better but not perfect.

The patient was followed at regular intervals by the operator until June 10, 1947. At this time there was no evidence of local recurrence and urinary incontinence was only present on occasions of extreme physical fatique. Shortly afterwards he moved from Rochester leaving no forwarding address. A report to us that he was examined elsewhere on January 2, 1952 and found to be well was evidently unfounded. On April 27, 1953 we finally contacted his wife who in-

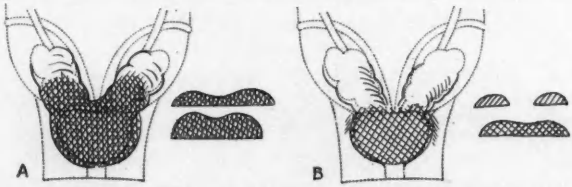


FIG. 2. *A*, prostate before stilbestrol therapy July 2, 1943. *B*, condition after supplementary orchiectomy July 17, 1945 and before radical prostatectomy September 9, 1945.

formed us that he died in Seattle of carcinomatosis on August 26, 1948 probably from a primary lesion of the prostate.

This case differed from the previous one in that the extension of the cancer to the region of the seminal vesicles was considerably greater and the regression due to control therapy was faster and more pronounced. The decision to perform a follow-up radical perineal prostatectomy in spite of very definite extension to the seminal vesicles with intervesicular plateau formation was greatly influenced by the marked response to control therapy. By so doing a criterion for the selection of patients for the combined therapy was violated. Although the patient was not cured the fact that he was quite comfortable during most of the 62 months he survived after treatment was started, suggests that he derived considerable benefit from it.

Case 3. B. F. C., S.M.H., 278670, aged 64 when first seen on April 14, 1948 complained of hesitancy, nocturia, recurrent hematuria and dysuria although a suprapubic prostatectomy had been performed elsewhere 3 years previously. His prostate was at least twice normal in size and the median furrow and notch were shallow. The lateral lobes were smooth but firm, being of second degree induration except at their bases where third degree induration was present, especially on the left side (fig. 3, *A*). As a result of this examination the clinical impression was benign prostatic hypertrophy plus inflammatory reaction. However on cystoscopic examination an irregular, bleeding, suspicious area was seen in the bladder just inside the vesical neck at about 4 o'clock. A diagnosis of adenocarcinoma probably of prostate was made from sections of this area. Treatment was complicated by the presence of moderately severe diabetes.

A bilateral orchiectomy performed on June 12, 1948 was supplemented by estinyl therapy, 0.05 mg. three times a day. By March 11, 1949 the right lobe of prostate had softened and regressed almost to normal size. Although the left lobe had decreased considerably in size, there remained a nodule of third degree induration covering a small area in the region of the base of the seminal vesicle (fig. 3, *B*). Since all studies were negative for metastases and on cystoscopic examination the area in the bladder had disappeared, a radical perineal prostatectomy was performed on March 15, 1949. A liberal cuff of the vesical neck was removed with the prostate and seminal vesicles. Pathological studies from prostate revealed carcinoma showing marked estrogen effect. The patient had good urinary control when discharged on estinyl therapy on April 4, 1949.

It would seem that although repeated blood phosphatase and radiographic

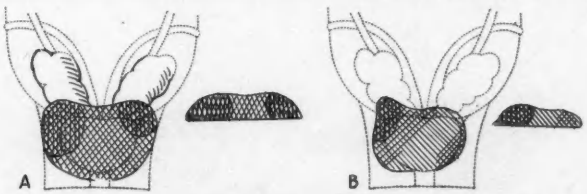


FIG. 3. *A*, situation at start of combined endocrine therapy June 12, 1948. *B*, condition at time of radical perineal prostatectomy March 15, 1949.

studies had been negative, metastasis had occurred before the radical prostatectomy was performed. Although at no time was there any evidence of a local recurrence, bone lesions were present within a year. The patient died of carcinomatosis on October 7, 1950. It now seems to us that the follow-up radical perineal prostatectomy is of very questionable value in those cases where extension beyond the vesical neck to the region of the trigone is present when the patient is first examined.

Case 4. G. O. B., S.M.H., 283183, aged 68, complained at the time of his first visit on September 20, 1948 of a gradually increasing frequency, nocturia, urgency and dribbling of 3 months' duration. The prostate was of third degree induration and greatly enlarged in its lateral and anteroposterior directions. Except for three very hard, discrete, nodular areas its posterior surface was relatively smooth. The median furrow and notch were absent. There was extension for a considerable distance up over each seminal vesicle with intervesicular plateau formation (fig. 4, *A*).

Following a bilateral orchiectomy on September 25, 1948, the patient was sent home on stilbestrol therapy with instructions to return at monthly intervals for observation. On March 14, 1949 the prostate had decreased to almost normal size and was of first degree induration. Second degree induration was present over the base of each seminal vesicle, more on the left than right, and between them there remained a plateau-like ridge of second degree induration (fig. 4, *B*).

A radical perineal prostatectomy was performed on March 17, 1949. The operator encountered marked difficulty in freeing the left seminal vesicle due to the presence of scar or carcinomatous tissue, probably the latter. He felt that extension beyond the operative field had occurred.

Active areas of carcinoma were found in sections from the prostatic and seminal vesicle portions of the surgical specimen. At the time of discharge, 30 days after operation, the patient occasionally dribbled slightly while at rest and considerably when under stress. Inasmuch as he was able to stop his stream completely during the act of voiding, we were confident that he would regain satisfactory control within a few weeks or months. Because of the relatively rapid progress of the disease the patient never returned for further observation. He died of carcinoma of the prostate on November 13, 1949.

In this patient at the time of operation there remained areas of second degree induration over the region formerly occupied by a well-defined intervesicular plateau due to extension from the prostatic carcinoma. In such cases the possi-

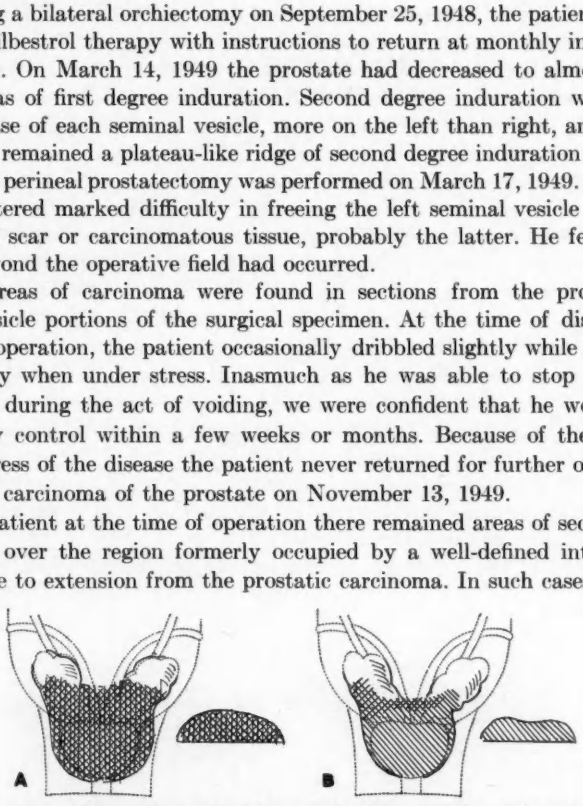


FIG. 4. *A*, prostatic involvement with extension to seminal vesicles when combined endocrine therapy was started September 9, 1948. *B*, induration due to cancer still present over seminal vesicles when radical perineal prostatectomy was performed March 14, 1949.

bilities of lymphatic and perineural extension or the presence of active tumor cells beyond the field of operation are such as to make the follow-up radical prostatectomy of very questionable value.

Case 5. V. M., S.M.H., 301085, aged 64 when first examined on August 29, 1949 complained of unusual fatique, decrease in size of stream, hesitancy and nocturia of 2 years' duration. Nothing of significance was found on physical examination except in the prostate gland which was moderately enlarged in all directions. Considerably more than half of the left lateral lobe was filled by a hard, irregular, fixed nodule that pushed its lateral border about 1.5 cm. beyond the confines of its normal contour and which extended medially almost to the median furrow (fig. 5, *A*).

Blood phosphatase and radiographic studies were negative for metastasis. Punch biopsy and Papanicolaou studies were positive for carcinoma.

The patient was placed on estinyl therapy 0.025 mg. three times a day and examined at monthly intervals until November 28, 1949. At that time the nodule seemed to have regressed sufficiently to permit its complete removal by radical surgery (fig. 5, *B*).

On cystoscopic examination the vesical neck simulated the picture of moderate collar hypertrophy. The residual urine was only 15 cc and there was no evidence of carcinoma extending into or beyond the vesical neck. On rectal palpation over the cystoscope an indurated nodule of moderate size was felt in the left lobe of prostate close to the apex. Although the outer border of the lobe was not well defined, the examiner thought there was a reasonable chance of getting around this area at operation.

On November 29, 1949 a radical perineal prostatectomy was performed. Considerable difficulty was encountered in developing a satisfactory line of cleavage between the lateral border of the left lobe of the prostate and the periprostatic tissue for a short distance just below the apex. However when this had been accomplished it appeared as though we had been able to get around the involved area.

His immediate postoperative course was very satisfactory. When he left the hospital 18 days after surgery his wound was healed and urinary control was good. He was sent home on estinyl 0.025 mg. daily, with instructions to return for a check on his condition at intervals of three months. A rectal examination on October 9, 1950 revealed a smooth operative field. His acid phosphatase was 5.1 and his alkaline 10.3 King-Armstrong units. On February 5, 1951 he returned

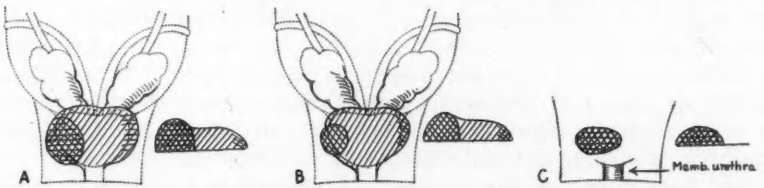


FIG. 5. *A*, extent of prostatic involvement when patient was first examined August 29, 1949. *B*, condition at time of radical perineal prostatectomy November 29, 1949. *C*, recurrence when first discovered February 5, 1951.

with a story of increasing fatigue and pain along the course of the right sciatic nerve. A recurrent lesion was found that corresponded somewhat in size and position to the one which was present in the prostate at the time of his first examination (fig. 5, *C*). At this time his acid and alkaline phosphatase readings were 6.4 and 16.6 King-Armstrong units respectively. Radiographic studies were negative for metastasis.

The bilateral orchiectomy performed on February 6, 1951 was supplemented with estinyl therapy 0.05 mg. twice daily. The regression of the growth and the relief of pain were only temporary. In August 1951 the recurrence had increased in size and his right sacro-iliac and sciatic pain had become more severe. The pelvic mass shrunk to the size of a pea following 700 mg.-hr. of radium applied per rectum in fractional doses. On October 17, 1951, because the patient's pain was increasing and metastatic lesions were present, a course of deep x-ray therapy was started. The relief from this was quite temporary.

Because his symptoms, blood phosphatase, and radiographic studies indicated steady progress of the disease, the right adrenal was removed on February 7, 1952 and the left 11 days later. The disease continued to progress gradually and death occurred on August 8, 1952.

Judging from the pathological character and extent of growth in the surgical specimen there might have been a better chance for its complete extirpation had the preoperative treatment consisted of a bilateral orchiectomy in addition to the estinyl therapy and had it been prolonged up to the point of maximum regression of the carcinomatous lesion.

DISCUSSION AND RESULTS

Because in some cases of carcinoma of the prostate in which the response to endocrine therapy has been especially satisfactory it may be very difficult to demonstrate the presence of residual carcinoma by means of microscopical studies of sections from the surgical specimen, the operator who is unwilling to proceed with radical surgery without positive histopathological support should make these studies before starting treatment. In 19 of our cases the clinical impression of carcinoma was confirmed by biopsy studies made either before or very shortly after endocrine therapy had been instituted. In 3 cases carcinoma was found in the surgical specimen even though biopsy studies were negative. Pathological studies of a biopsy specimen obtained from the first patient in this series on his initial visit were typical of carcinoma of the prostate. Following castration and estrogen therapy the radical operation was performed 42 months later. A study of many sections from the surgical specimen repeatedly showed connective tissue formations very similar to those found in cancer of the prostate but the epithelial cells were either absent or so changed that a positive diagnosis could not be made. It is our belief that had a serial section of the whole surgical specimen been made, carcinoma cells would have been found. In 2 recent cases a clinical impression upon rectal examination by at least two of our senior staff, repeated positive Papanicolaou studies by a cytologist especially skilled in this particular field, and regression and softening of the suspected area following

endocrine therapy, all pointed so strongly towards carcinoma that a radical perineal prostatectomy was performed.

Pathological studies of a considerable number of sections from each surgical specimen showed the pattern described above but no typical normal carcinoma cells were found. It is interesting that the cytologic studies in these cases showed progressive effect of the endocrine therapy upon the malignant cells which were very plentiful when the patients were first examined. In one case after 6 months of therapy, the malignant cells completely disappeared and remained absent until the radical operation was performed 2 months later. While the malignant cells did not completely disappear in the second case, they did decrease greatly in number and show marked estrogen effect before the operation.

In our opinion, all patients who have had a radical prostatectomy for cancer of the prostate gland should continue a routine course of some type of estrogenic therapy for a very long time after operation, regardless as to whether they were treated in the manner presented above or belonged to the more fortunate group, in which because of the size and location of the carcinomatous nodule, a preliminary course of endocrine therapy did not seem necessary. It is not always easy to convince some of these patients, who are feeling well and know that the organ which was the source of their trouble has been completely removed, that they must continue estrogen therapy even though at times it may cause some discomfort. However, the reasons for the postoperative continuance of estrogen therapy are so obvious and valid that even the most stubborn patient can be convinced of its necessity without creating a cancer phobia, if patience and discretion are exercised in their presentation.

When the clinical impression of carcinoma of the prostate has been definitely confirmed by a positive punch biopsy study in a patient who qualifies for the follow-up radical perineal prostatectomy providing the response to hormone control treatment proves to be successful, bilateral orchiectomy plus estrogen is the preoperative therapy of choice. As shown by Nesbit and Baum, the survival rate was better where these two types of endocrine therapy were combined than when either was used alone (table 1). Furthermore it seems to us that the cleavage lines are more easily developed and the whole operative procedure somewhat facilitated in the presence of a previous bilateral orchiectomy. Finally any lapse on the part of the patient with reference to his postoperative estrogen therapy might be covered, for a time at least, by the absence of the testicles.

The results of endocrine therapy plus a radical perineal prostatectomy in our first 25 cases have been most encouraging. In all these cases treatment was started 36 months or more before the material for this report was summarized. The longest time that had elapsed since endocrine therapy was started was 130 months, the shortest 14 months and the average time was 61.2 months. The average time after prostatectomy was 47.6 months, the longest 89 and the shortest 5 months. There were 4 deaths within 36 months from the time that the therapy was started. In one where carcinomatous tissue was left in the seminal vesicle region (case 4) the patient died of cancer 14 months after treatment was started and 5 months after surgery. Another patient died of coronary

TABLE 1. *Percentage survival at 6 month intervals of a series of 25 selected cases of advanced carcinoma of prostate without metastasis at time of first visit which were treated by endocrine therapy alone or combined with radical perineal prostatectomy as compared to a control series of similar cases (Nesbit and Plumb) treated by methods in use before introduction of endocrine therapy.*

TYPE OF THERAPY	MONTHS						NUMBER OF ELIGIBLE CASES	PER CENT DEAD NOT DUE TO CA.
	6	12	18	24	30	36		
Control (Nesbit and Plumb)	72.0	54.0	39.0	32.0	25.0	20.0	273	—
Stilbestrol (Nesbit and Baum)	90.7	82.2	75.6	69.1	56.2	49.7	143	34
Castration (Nesbit and Baum)	91.6	84.9	74.0	65.9	62.2	53.4	239	26
Castration and Stilbestrol (Nesbit and Baum)	95.6	89.3	82.3	76.0	76.0	66.0	159	37
Endocrine therapy plus the radical perineal prostatectomy (Scott)	100	100	92.0	88.0	84.0	84.0	25	25
Total cases							839	

thrombosis 14 months after therapy was instituted and 8 months after prostatectomy. A very careful autopsy study revealed neither local recurrence nor metastasis. In the third patient (case 3) who died of metastases 28 months after the start of treatment and 18 months after his radical operation there was no evidence of local recurrence. The fourth patient who developed a reccurent lesion with metastasis was not greatly benefited by bilateral orchiectomy, deep x-ray therapy and bilateral adrenalectomy, dying of carcinomatosis 35 months after therapy was started.

Of the patients who survived 3 years or more after treatment was started 5 are known to be dead. There were two deaths due to recurrent and metastatic carcinoma from the prostate. One of these patients who died 82 months after start of therapy was not placed on estrogen therapy until a local recurrence was discovered 56 months after his prostatectomy (case 1, C). The other patient died of generalized carcinomatosis 62 months after he was placed on treatment. A third patient died of a primary carcinoma of the stomach 64 months after treatment was instituted while the fourth died of coronary disease 58 months after therapy was started. A fatal airplane accident 47 months after start of therapy resulted in the death of the fifth patient. In another patient who refused to take postoperative estrogen therapy and in whom a small, local, recurrent nodule was suspected 46 months after treatment was started, the area completely disappeared following orchiectomy and needle radiation therapy. When last seen 10 months later all studies were negative for cancer. Of the remaining 6 patients who have been followed less than 36 months one has developed a local recurrence and metastases.

Before attempting to evaluate the relative effectiveness of endocrine therapy plus the follow-up radical perineal prostatectomy in the treatment of carcinoma of the prostate, it seems advisable to emphasize that its field of usefulness is

definitely restricted. It is our belief that in early carcinoma of the prostate where the lesion is contained within the confines of the prostate, the radical removal of the gland, seminal vesicles along with their posterior fascial covering should be accomplished as soon as possible after the diagnosis has been made. As pointed out previously the patients for whom the combined therapy offers the most hope are very carefully selected from the group of advanced carcinoma of the prostate who were without metastasis when first seen.

Fortunately, there is now available sufficient reliable data to permit a very satisfactory evaluation of the relative effectiveness of the various types of therapy used in the treatment of patients with advanced carcinoma of the prostate who were without metastasis when first seen. As a control series we have the report by Nesbit and Plumb on the survival rate at 6 month intervals on 273 of these cases which were treated by the methods in use before the introduction of endocrine therapy and followed for 36 months after their first visit. Based upon case material supplied by members of the Urosurgical Society, Nesbit and Baum in 1952 reported the survival rate at 6 month intervals for 36 months on a series of 540 cases of advanced carcinoma of the prostate without metastasis when first seen which were treated by the various types of endocrine therapy in common use to-day. To the above we have added our series of 25 cases which were treated by the combined therapy (table 1). One cannot examine these results without experiencing a feeling of profound gratitude for the progress that has been made in the treatment of carcinoma of the prostate during this last decade. Whereas the survival rate for 36 months was but 20 per cent in the control series, it was 66 per cent in the castration and stilbestrol group and 84 per cent in the patients who were treated by the combined endocrine and radical prostatectomy method. While we realize it would be unwise to attach too much significance to the results of a comparative study in which one group is much smaller than the others, it is interesting to note that the per cent of deaths not due to cancer in the small group was very close to that of the other groups.

We think that our results are sufficiently encouraging to warrant further trial of this therapy. Even if in our future cases the carcinoma is not as satisfactorily controlled, we believe that this treatment in most instances, where judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease. As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction. Furthermore, the introduction by Vest of the traction suture method of anastomosing the vesical neck and the membranous urethra has done much to prevent the incontinence that occasionally resulted from this type of surgery.

CONCLUSIONS

The results obtained in the first 25 of a series of 31 selected cases of advanced carcinoma of the prostate that were treated by endocrine therapy combined with a follow-up, radical perineal prostatectomy and followed three years or more have been presented and discussed.

While this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results to date warrant a further trial of this therapy, not only by us, but by others.

REFERENCES

COLSTON, J. A. C. AND BRENDLER, H.: Endocrine therapy in carcinoma of prostate; preparation of patients for radical perineal prostatectomy. J.A.M.A., **134:** 848–853, 1947.

NESBIT, R. M. AND BAUM, W. C.: Endocrine control of prostatic carcinoma; clinical and statistical survey of 1,818 cases. J.A.M.A., **143:** 1317–1320, 1950.

NESBIT, R. M. AND PLUMB, R. T.: Prostatic carcinoma; follow-up on 795 patients treated prior to endocrine era and comparison of survival rates between these and patients treated by endocrine therapy. Surgery, **20:** 263–272, 1946.

PARLOW, A. L.: Advanced cancer of prostate; consideration of value of radical prostatectomy in selected cases. New York State J. Med., **45:** 383–387, 1945.

PARLOW, A. L. AND SCOTT, W. W.: Hormone control therapy as a preparation for radical perineal prostatectomy in advanced carcinoma of the prostate. New York State J. Med., **49:** 629–634, 1949.

SCOTT, W. W.: An evaluation of endocrine control therapy followed by radical perineal prostatectomy on selected cases of advanced prostatic carcinoma. Cancer, **6:** 248–265, 1953.

SCOTT, W. W. AND BENJAMIN, J. A.: Role of bilateral orchiectomy in treatment of carcinoma of prostate gland; report of 82 cases. Bull. New York Acad. Med., **21:** 307–332, 1945.

SCOTT, W. W. AND PARLOW, A. L.: Evaluation of hormonal therapy followed by radical perineal prostatectomy on selected cases of advanced prostatic carcinoma. J. Urol., **65:** 1093–1107, 1951.

VALLETT, B. S.: Radical perineal prostatectomy subsequent to bilateral orchiectomy. Delaware State Med. J., **16:** 19–20, 1944.

VEST, S. A.: Radical perineal prostatectomy, modification of closure. Surg., Gynec. & Obst., **70:** 935–937, 1940.

APPRAISAL OF PRESENT METHODS OF TREATMENT OF ADVANCED PROSTATIC CANCER

W. W. SCOTT

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Until receipt of the program for this meeting and particularly until I had read the titles of the papers constituting this symposium, I had little idea as to what I should present under the title which Dr. Heckel assigned to me.

Dr. Scott has just presented to you an evaluation of hormonal therapy followed by radical perineal prostatectomy in selected cases of advanced carcinoma of the prostate. You will recall that Dr. Colston and Dr. Brendler, of our Institute, presented a preliminary report on this subject in an issue of the J.A.M.A. for 1946. Whereas I believe that Dr. Scott has handled the subject in a splendid fashion and has demonstrated the merits of this regimen in certain selected cases, I am of the opinion that in this instance, as well as in all instances of studies involving the treatment of cancer of the prostate, insufficient attention has been paid to the "biological potential" of the cancer. Admittedly, we have used almost all of the yardsticks available to us at present, but none really tell us the degree of malignancy of any given cancer, and hence are of little prognostic value.

May I attempt to illustrate what I am driving at by referring to two patients recently seen again at the Brady Institute: The first, a man aged 75, was seen in 1928 with signs and symptoms of a benign obstructing prostate. A simple perineal enucleation was carried out at that time, and sections made on the tissue removed revealed adenocarcinoma. Within one year, although there were no signs of metastasis, examiners felt that the cancer had extended beyond the capsule of the gland and that total prostatectomy was not indicated. The patient was lost track of until approximately 6 weeks ago when he returned to the dispensary in acute retention. On rectal palpation the prostate was large and nodular. It was judged cancerous and definitely inoperable. Serum acid phosphatase levels were normal and x-rays revealed no evidence of metastasis. A transurethral resection for relief of obstruction was done and sections on this tissue showed adenocarcinoma indistinguishable from that removed 25 years previously. In any series, this would be a 25 year cure, no matter what was done.

A second case is similar. The patient, seen by Dr. Colston in 1941, was believed to have an early operable prostatic cancer. A perineal biopsy revealed a small nodule which on frozen section proved to be adenocarcinoma. A total prostatectomy was done at the same sitting and yet multiple permanent sections failed to reveal any cancer, indicating that the biopsy was generous and had removed the entire cancerous nodule. The patient did exceptionally well until 1951. As a matter of fact, he continues to do well, and yet since 1951 his bones are seen to be riddled with cancer and his serum acid phosphatase is elevated. Endocrine treatment is now being given.

Based on these two cases alone, one might be inclined to think that adenocarcinomas were less malignant than undifferentiated prostatic cancers, and yet a previous attempt at correlating the length of survival with cell types has led me to believe that no significant relation exists and that one cannot predict on the basis of cell type the response to any particular form of therapy.

I will be very much interested to hear the follow-up reports to be presented by Dr. Baker and by Dr. Harrison on the subject of bilateral adrenalectomy for advanced prostatic cancer. You will recall their preliminary reports of last year. Since last year we have done no more bilateral adrenalectomies. As a matter of fact, we have only performed two for prostatic cancer, one surviving a few months and one dying within the last two months, some 15 months after both adrenals were removed. Recently, these two cases were presented at the clinical pathological conference held weekly in our Department of Pathology by Dr. Arnold Rich. One thing in particular interested me. Whereas there was definite evidence in certain areas of the prostate that certain cancer cells had undergone atrophy, immediately adjacent to these areas were areas of perfectly good cancer which seemed to be uninfluenced by anything that had been done to the patient. Furthermore, sections of untreated prostatic cancer in patients before the days of endocrine management were presented and often showed identical changes. I do not mean for a minute to leave you with the impression that I think that prostatic cancer has not been influenced by endocrine manipulations or that further advances will not be made. If I thought this, I would discontinue many studies currently in progress involving endocrine relations in prostatic growth. I do mean to emphasize, however, that the nature of our controls leaves much to be desired.

Recently, in completing a monograph on *The Surgery of the Adrenal Glands* as one of the American Lecture Series in Surgery, I reviewed all the cases of adrenalectomy done to date, not only for prostatic cancer but for cancer of the breast as well. Time does not permit review of these data, however, I will read to you the most recent results in a series of 10 patients adrenalectomized for prostatic cancer and reported by the Memorial Hospital group: "Three died in the immediate postoperative period, one from cerebral hemorrhage (2 days), one from carcinomatosis (11 days) and one from myocardial infarction (21 days). Six of the remaining seven died within 33 to 294 days after adrenalectomy, two from adrenal insufficiency and four from cancer." The remaining patient was living at the writing of this addendum, his 159th postoperative day. Quoting further: "All seven patients had temporary subjective improvement varying from 14 to 210 days, averaging 82 days. Only two of the seven had objective improvement lasting 90 and 133 days. The most striking beneficial response to adrenalectomy was relief of pain." There has not been a publication from the Huggins laboratory on adrenalectomy for prostatic cancer since that of Huggins and Bergenstal, to be found in *Cancer Research* for 1952, and the results in this series of 7 patients are quite comparable to those of the Memorial Hospital group. Of the seven there was one postoperative death, and they judge that three of the remaining six had a clinical remission of the disease of considerable magnitude. One patient

died of acute pulmonary edema 49 days after adrenalectomy. The remaining four had been observed for periods of 4½ to 9 months at the time of the report. Quoting them: "Perhaps the most striking observation has been the immediate and persistent relief of crippling pain in the bones." In conversation with Dr. Huggins since this report, I have learned that he is performing fewer and fewer bilateral adrenalectomies for prostatic cancer and more and more for cancer of the female breast.

Unfortunately, in most studies to date an insufficient amount of time and effort has been spent in determining the mechanism of action of bilateral adrenalectomy, and it is my feeling that until such is done, little further advance will be made. During the past year there has been further evidence to support the statement which I made at this same meeting in 1952 that cortisone, so necessary in the maintenance of the bilateral adrenalectomized human, is metabolized to androgen. Again this is hard to reconcile with theories which assign improvements following adrenalectomy to androgen withdrawal. Cortisone alone has been as effective at times as adrenalectomy. At present it is my opinion that adrenalectomy for cancer of the prostate and breast is empirical, as Huggins suggests the administration of androgen or estrogen is for advanced breast cancer in the female. If results were better than they are to date, one would be justified in advising this procedure in the individuals hopelessly afflicted with these cancers. In that they are not, it is my belief that these should be considered as research tools and only carried out in institutions equipped for research.

The same holds true for hypophysectomy. One year ago I reported to you on the results in 3 cases of disseminated prostatic cancer subjected to hypophysectomy. Since then, two more cases have been studied. One of these died within a few days after operation, and the other is alive and clinically in fair condition some 6 months after operation. To date total hypophysectomy has not been possible, probably because of the difficulties of exposure, and we are considering ablation of that portion of the pituitary which cannot be removed by radioactive means. In attempting to evaluate the procedure to date, I can simply say that in the two individuals with close to total hypophysectomy, one living 5 months and coming to autopsy and one alive at present, the effects have been comparable to those observed following adrenalectomy. In one whose testes were intact at the time of hypophysectomy, the effects were strikingly like those following castration. We do not recommend the procedure to any of you, but will continue to use it in selected cases in an effort to learn more about this disease.

What the future holds, no one knows, but I am firm in my belief that we will make more progress by carefully studying endocrine effects on prostatic growth in the animal, with careful clinical studies when indicated, than to attempt to draw conclusions from a statistical study of a huge series of patients subjected to any one of a number of endocrine procedures. As I have attempted to point out in an article in the 1952 *Transactions of the Western Section of the American Urological Association* entitled, "What Makes the Prostate Grow," much more must be learned concerning the effects of estrogen withdrawal, estrogen being a secretion of the testis as well as androgen. Much more must be learned of the

precise nature of the chemical substances liberated by the testes and by the adrenals. If we were to know more, we could predict with a fair degree of accuracy what analogs or, in other words, closely related steroids, would act as inhibitors of circulating biological gonadal and adrenal steroids. If we were to know more about the effects of the pituitary on benign and malignant prostatic growth, we could design better experiments directed towards chemical inhibition of pituitary action.

The road ahead is long and hard. Someone might make a discovery tomorrow which might put us ahead many years, but I doubt it. I do not think this is a pessimistic attitude but a realistic one. A pessimist would not be in this field. Being a realist, I think that for the immediate future we, as urologists, should make every effort to educate the public and the physician in the early recognition of prostatic cancer, at a time when it is operable and at a time when total prostatectomy in the hands of most offers a 50 per cent chance of 5 year survival without cancer. In the meantime, many of us in our laboratory will endeavor to unravel some of the problems discussed. These largely revolve around the early chemical detection of prostatic cancer, the biological potential of any given tumor, the metabolic action of steroids and the nature and action of competitive steroids.

We have made no progress in the chemical detection of early prostatic cancer, although we are continuing a program of fractionation and identification of urinary steroids hoping to find some one specific for prostatic cancer.

For some time we have considered and have now initiated a program in which we are attempting to correlate survival of human prostatic cancer in the anterior chamber of the guinea pig eye with the degree of malignancy as determined by the clinical course of the disease—a search for the "biological potential."

To date we have been unable to demonstrate any *in vitro* effects of androgens or estrogens on human and animal prostatic slices. We have observed, however, a profound differential *in vivo* inactivation of androgens by the altered liver. This is contrary to our findings using estrogens.

Lastly, a lengthy program is in progress aimed at finding analogs of androgens.

In a few years we may have something to report.

LATE RESULTS OF BILATERAL ADRENALECTOMY FOR ADVANCED CARCINOMA OF THE PROSTATE GLAND

WILLIAM J. BAKER

One year ago, a report was given to this Association on bilateral adrenalectomy for 10 patients whose carcinoma of the prostate gland and symptoms had not been adequately controlled by open prostatic surgery or revision of the obstructive vesical neck, estrogens, bilateral orchiectomy, with and without deep roentgen therapy, and oral cortisone. All of these patients were bedridden and required some form of opiate for their pain and discomfort. All patients had had a tissue diagnosis of cancer of the prostate gland. All patients had bone metastases. There was no immediate operative mortality. There was no difficulty in the postoperative management of these Addisonian individuals.

We have been impressed with the comfortable states of the majority of these patients after bilateral adrenalectomy. Only one patient failed to get relief from the procedure. All, except two, became ambulatory and euphoric. To be sure, there has been a recurrence of pain in all except one patient. He is alive and well almost 10 months. The recurrent pain has usually been less severe than the original pain. The patients who require small amounts of analgesic for their recurrent pain, have led a much more comfortable existence than they did before bilateral adrenalectomy. In 2 patients, whose pain returned, a short course of deep x-ray therapy over the painful regions, gave almost complete relief. X-ray therapy over these same regions, before bilateral adrenalectomy, had given no relief.

The youngest patient in this group was 47 years, the oldest was 76 years. The patients who have lived the longest after bilateral adrenalectomy were 57, 58, 60 and 61 years old. The age of the patient could not be related to the amount of relief which was obtained from metastatic pain. The patient who obtained no relief from the procedure was 59 years old.

Adrenalectomy for cancer is predicated on the fact that the adrenal gland is involved in the growth of neoplastic tissue. It is known that people with cancer have abnormal amounts of normal adrenal steroids. It is also known that people with cancer have steroids that are not found in other people. However, after bilateral adrenalectomy in patients with advanced cancer of the prostate gland, serial x-rays of osseous lesions, serial acid and alkaline phosphatase determinations, serial rectal examinations, serial body weight and hemoglobin determinations and serial androgen values have furnished us no evidence that the prostatic cancer or its metastases have been inhibited. As far as we can ascertain, the cancer continues to grow at its usual rate. Figure 1, *A* is the picture of obvious metastastic bone lesions of one of these patients before bilateral adrenalectomy. Figure 1, *B* is a picture of the same lesions 7 months after bilateral adrenalectomy. Figure 2, *A* is the x-ray picture of obvious metastatic bone lesions of another patient before bilateral adrenalectomy. Figure 2, *B* is a repeat picture of this same patient 9½ months after bilateral adrenalectomy. Figure 3 is the final

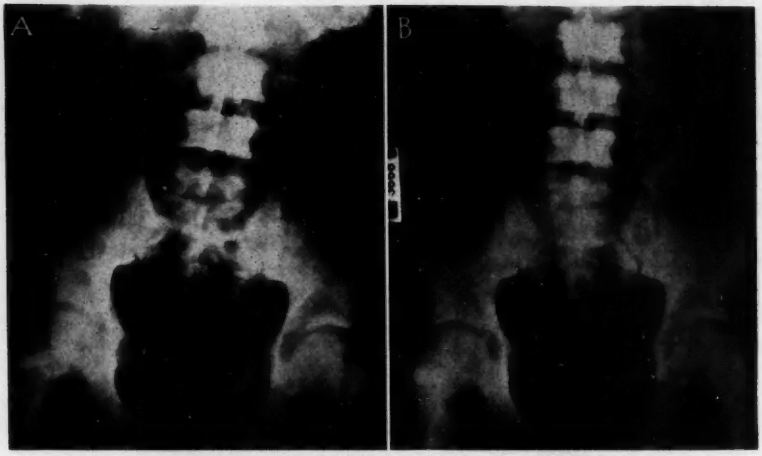


FIG. 1

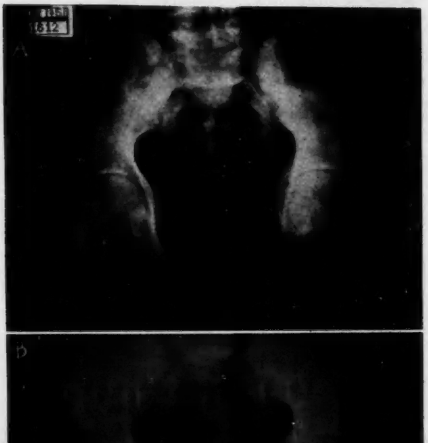


FIG. 2

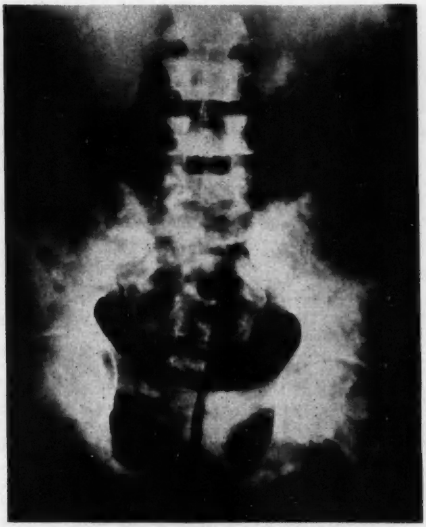


FIG. 3

picture of this patient's bones just before he died, or 13 months after bilateral adrenalectomy. The metastatic bone lesions of these two patients were obviously not retarded. It is certain that no bone metastases disappeared in these pictures. It must be admitted that, occasionally, bony metastases seem to grow more sclerotic after adrenalectomy. We have never seen them become smaller or disappear.

What about the life expectancy of the man with advanced prostatic cancer, who has had bilateral adrenalectomy? Tables 1 and 2 show that only two out of eleven of our patients are alive. The longest time that any of our patients lived after this procedure is 1 year, 1 month, 11 days. One patient is alive 1 year, 22 days after the procedure. This man has recently complained of severe pain which requires Demerol for control. Another patient is alive 9 months, 20 days. He had minimal persistent discomfort after bilateral adrenalectomy. A course of deep roentgen therapy caused complete disappearance of the discomfort. He takes no sedatives or analgesics, is ambulatory, euphoric and working. The other 9 patients lived from 1½ months to 1 year, 11 days. Thus, it can be seen that there has been no striking prolongation of life in this group.

All of our patients have died relatively suddenly. They were ambulatory one day and in a terminal state the next day. Most of them have become weak, apathetic and finally comatose, all within a very few hours. Blood chemistry studies have not revealed striking changes even on the day of death.

Four complete autopsies have been performed on patients who have had bilateral adrenalectomy for advanced prostatic cancer. No residual adrenal tissue was found in these four bodies. No tissue had been spared from invasion by the cancer cells.

TABLE 1. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
T. P., Negro, St. Luke's Hospital	48	6 months 1 day	Needed codein last month of life	Collapsed suddenly and died in 2 hours	Generalized carcinomatosis. No other adrenal tissue found
I. S., White, Cook County Hospital	59	5 months 3 days	Demerol the last 4 months of life	Generalized edema and coma last 2 days of life	Generalized carcinomatosis. Metastases in pituitary gland. No other adrenal tissue found
C. G., Negro, Cook County Hospital	61	1 year 1 month 11 days	Required codein and Demerol last 3 months of life	Developed very severe anemia. Many transfusions. Always euphoric. Sudden death	No autopsy
B. T. W., Negro, Cook County Hospital	47	3 months 5 days	Demerol last 2 months of life	Died suddenly. In coma for 2 hours	Generalized metastases. Large metastatic growth around old gunshot wound of hip. No adrenal tissue found
J. M., Negro, Cook County Hospital	57	1 year 1 day	Demerol last 6 weeks of life	Always had troublesome gas "on stomach". Died during sleep	Generalized metastases. Each ureter was partially obstructed by a metastatic tumor. Original blood pressure 220/110. Adrenalectomy did not alter hypertension. No adrenal tissue found

TABLE 2. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
A. N., White, St. Luke's Hospital	65	6 months 9 days	Demerol required last 4 months of life	Died very suddenly. Ambulatory until day of death	No autopsy
S. G., White, St. Luke's Hospital	76	5 months 9 days	Codein required last 2 weeks of life	Sudden collapse and death while campaigning for Taft	No autopsy
E. N., White, Cook County Hospital	60	Still alive and well. 1 year 22 days	Has fleeting pains. Takes no sedatives		
C. B., White, St. Luke's Hospital	62	1 month 15 days	No sedatives required	Lethargic and catatonic for 6 weeks. Slow death	No autopsy
J. Z., White, St. Luke's Hospital	54	3 months 10 days	No relief from metastatic pain	Sudden death. One hour of coma	No autopsy
T. T., Japanese, Cook County Hospital	58	Still alive and well. 9 months 20 days	No sedatives required		Complete relief from pain after x-ray therapy following adrenalectomy

It can be seen that the evaluation of this procedure is made entirely on the subjective response of the patient. The relief of pain is usually striking. The patients who have been bedfast because of pain, feel better almost immediately and want to get out of bed in a few days. Their appetite becomes ravenous and the replacement therapy with cortisone usually produces an euphoric state. The occasional patient will be rehabilitated enough to resume his former work. Most of our patients have never returned to their work.

The past year has brought to our attention that the patient who fits our indication for this procedure has become very scarce.

Cook County Hospital is a haven for end pathology. It has furnished us only one patient for our series. Four excellent residents have endeavored to find such patients. St. Luke's Hospital has not furnished a single private patient for our series. One wonders whether prostatic cancer is changing its biological behavior.

It is believed that bilateral adrenalectomy is an excellent procedure for the relief of metastatic pain from advanced prostatic cancer of patients whose pain is not adequately controlled by castration, estrogens, deep roentgen therapy or oral cortisone.

In conclusion, the thought should be left with you that there is evidence that some cancers of the prostate gland seem to be independent of androgens and the search for related stimulating or inhibiting factors should be continued diligently.

7 W. Madison St., Chicago 2, Ill.

THE TREATMENT OF PROSTATIC CARCINOMA WITH RADIOACTIVE COLLOIDAL CHROMIC PHOSPHATE (P^{32}). PRELIMINARY REPORT

CARL RUSCHE AND HENRY L. JAFFE

From the Departments of Surgery (Urology) and Radiology (Therapeutic), University of Southern California School of Medicine, and Department of Radiation Therapy, Cedars of Lebanon Hospital, Los Angeles

Radiation therapy by means of radium and roentgen rays has been used as a form of treatment over a period of many years for certain patients with inoperable prostatic carcinoma. The results reported by Pasteau, Young, Barringer, Deming Bugbee, Bumpus, and others, included treatment techniques employing deep x-ray therapy externally as well as the interstitial use of radium and radon alone or combined with external radiation. The prostatic cancer when radiated often showed definite reduction in the tumor mass. Occasionally complete eradication of disease has been reported. More recently when intensive x-ray and radium treatment was employed, most of the treated tumors showed some response. At the same time, with the larger x-ray and radium doses the incidence of complications resulting from the effects of radiation on the surrounding normal tissues increased in number and severity. Bladder irritation and ulceration and damage to the adjacent intestinal loops resulting in radiation colitis, ileitis, and sometimes stricture formation, made the necessary intensive x-ray and radium treatment for this condition impractical. Flocks, Kerr, Elkins, and Culp (1952) have reported the results of treatment of this disease by the interstitial injection of radioactive gold (Au198). When radioactive gold in colloidal solution was injected into the site of the prostatic cancer, the authors reported that 90 per cent of the material remained at the site of injection, and that it was apparently nontoxic. Improvements in technique seem to have done away with the moderate rectal irritation which they observed early in their studies. Local spread of the material is induced by the use of hyaluronidase, and the general spread by absorption into the blood is inhibited by epinephrin. One millicurie of radioactive gold per cubic centimeter of tissue represents approximately 65,000 equivalent roentgens of beta dosage together with some six to seven thousand units of gamma roentgens. Since the maximum range of the gold particle is only 3.8 mm. and because about 95 per cent of the effective rays are beta rays, very intensive radiation of the tumor tissue is possible without danger of damage to the surrounding normal tissues. About one millicurie of colloidal gold-198 is injected into the prostatic area for each gram of estimated weight. This is accomplished by a special lead covered syringe with a rachet device permitting considerable pressure to be applied and at the same time limits the amount given to a volume as selected by the operator, ranging from 1 to 5 cc. The first 50 cases treated by these authors and followed from 7 to 17 months had previously been treated by hormones and other procedures without success. The results as reported in the *Journal of Urology* in August 1952, are as follows:

Average age	69
Previous treatment	29
Complications (all rectal)	15
Alive without clinical disease	27
Alive with clinical disease	8
Dead without clinical disease	7
Dead with clinical disease	8
Biopsied after Au	
Positive	27
Negative	10

We were impressed with the results reported by the University of Iowa group, but there were certain features of the gold treatment which we considered unsatisfactory. First, the short half-life of radioactive gold (2.7 days) does not make it practical for shipping from the Atomic Energy Commission plant at Oak Ridge to the West Coast. A good deal of the material is dissipated by the elapsed time in shipping before it can be used in patients. The second disadvantage of radioactive gold is the presence of gamma rays. These probably do not add sufficient advantage for therapeutic purposes but do definitely present a health hazard to personnel handling the material because of their long range and high degree of penetrability. This necessitates heavy lead shielding (32 lb. lead pot necessary) in shipping, which increases the cost of air freight. The gamma rays in radioactive gold also increase the need for shielding in the operating room while the material is being prepared by the radiologist. It requires a special lead-lined syringe for the surgeon in order to protect his hands. To allow for the physical decay during shipping, it is necessary to order a larger quantity of the material. This added quantity requires additional lead shielding in shipping and further increases the cost of air freight. The possibility of bone marrow depression by the gamma radiation is another disagreeable factor. Recently, 4 cases have been reported by Botsford, Wheeler, Newton and Jaques (1953), where bone marrow depression occurred from doses of radioactive gold injected intraperitoneally and intrapleurally in ranges over 50 millicuries.

We sought a radioactive substance that could be made in colloidal form with a particle size large enough so that it would not permeate the blood vessels and thus enter the general circulation. We wanted a substance that would have pure beta radiation so that there would be little or no damage to adjacent normal structures and would require a minimal amount of shielding for shipping and safe handling in the operating room. We desired to obtain a substance with a longer half-life so that physical decay would not be rapid, and it might be possible to keep the material on hand for use as needed.

Radioactive colloidal chromic phosphate seemed to fulfill all of these requirements. It is made in the laboratory from the soluble form of radiophosphorus (P^{32}). It has a physical decay or half-life of 14.3 days. It is a pure beta ray emitter with energy of 0.7 million electron volts. It has a range of 8 mm. of maximum penetration in water or tissue, and it delivers a total dose in roentgen equivalents physical (REP) of 885,000 REP to 1 gm. or cc of tissue containing 1 millicurie of the isotope completely disintegrating. The shielding required to protect the

surgeon's hands is minimal since beta rays are easily filtered out by plastic, glass and aluminum. The rubber gloves worn by the operator are sufficient to protect the skin of his hands from contact with the beta rays. If there is any contamination of instruments, linen, operating room table or floor, the radioactive material may easily be washed off by means of a detergent soap and water. The handling of the patient postoperatively is safer because there are no long range gamma rays which may cause injury to visitors or to adjacent patients in wards. The effect in the tumor area is that of millions of beta particles of the material each acting as a radiation source which extends its effect over a distance of 8 mm. Theoretically, if one could distribute the material uniformly throughout the cancer area, it would be possible to destroy all of the cancer tissue without injuring the adjacent normal tissues.

We have seen no deleterious effects from the use of this isotope as far as the general condition of the patient or the bone marrow is concerned. We have monitored the excreted urine and find that 1½ per cent of the injected material is excreted in 24 hours, and only an additional 1 per cent is excreted for the next six days. This shows that 97.5 per cent of the material stays at the site of injection. Samples of the patient's blood and bone marrow failed to reveal any radiation activity in these tissues. Very small amounts of radiation could be picked up over the spleen, kidneys, and liver. This amount of radiation is not considered large enough to cause any damage to these organs.

When colloidal chromic phosphate was injected into the prostate of dogs and they were sacrificed between four to five months, the following changes were noted. The entire prostate was reduced in size, the tissue was firm, avascular, and failed to show any radiation activity. The liver, spleen, kidneys, and lungs showed no deleterious effect or radiation activity. Sagittal sections through the prostate close to the site of the implanted radioactive material revealed scarring and inflammation with areas of necrosis. However, it was remarkable how restricted the effect was in the prostate. The histological examination disclosed a diffuse increase of fibrous connective tissue throughout the organ. The only tubules that showed any effect were in the immediate region of the implanted chemical (figs. 1 and 2, courtesy Dr. Harry Goldblatt). Microscopic sections on liver, kidney, spleen, lungs, and pelvic lymph glands showed no significant changes.

It is the purpose of this report to evaluate the therapy and clinical results of the treatment of 28 cases of carcinoma of the prostate treated with colloidal radioactive chromic phosphate during the year 1952.

Patients with carcinoma of the prostate may be divided into three stages of the disease, dependent upon the clinical findings: 1) when the cancer is limited to the prostate itself; 2) when the tumor extends beyond the prostatic capsule into the periprostatic tissue and regional lymph nodes; 3) when there are distant metastases. Unfortunately, the number of cases of carcinoma of the prostate in stage one is small, approximately 5 per cent. In these patients the disease is discovered either by a routine rectal examination or at the time of transurethral resection. The treatment of choice in this stage is total prostatectomy.

A much larger number of patients present themselves in the second stage of

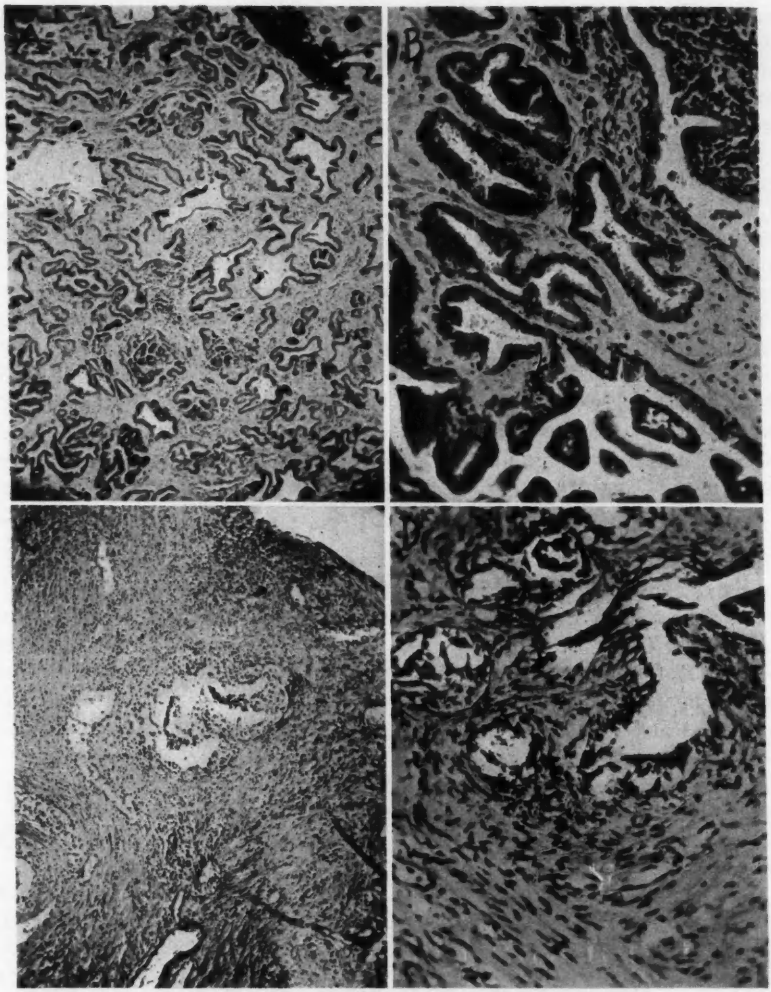


FIG. 1. *A*, low power photomicrograph of section of dog's prostate 1 cm. from site of injection. *B*, high power (×430) same section. *C*, low power photomicrograph of a section of dog's prostate at site of injection. *D*, high power (×430) same section.

the disease. Symptoms of bladder neck obstruction are usually present, and the examination reveals a fixation of the gland with extension of the lesion along the seminal vesicles. Occasionally regional lymph nodes are involved. However, no evidence of distant metastases is demonstrated. The treatment suggested in these cases has been transurethral prostatic resection and hormonal therapy. Approximately 50 to 60 per cent of the patients with prostatic cancer present themselves in the second stage of the disease. The patients seen in the third stage

of the disease have all the findings of those in the second but in addition have distant metastases (osseous and lungs). The treatment in these patients has been transurethral resection of the bladder neck, estrogens, orchiectomy, and high voltage radiation for relief of pain.

The use of certain radioactive isotopes in the detection and treatment of malignant tumors has stimulated interest and investigation into the procedure of introducing radioactive material directly into the prostate gland in the hope of curing cancer. Colloidal radioactive gold (Au198) was utilized by Flocks with encouraging results. We have chosen colloidal chromic phosphate because of the pure beta rays. The radiation is localized and intensive, with 7 to 10 times the energy of gold, and there is no deleterious effect upon the surrounding tissue. Chromic phosphate has, in addition, a half-life of 14.3 days, and 100 per cent of the energy released is the form of beta radiation with a maximum range of 8 mm. Therefore, the intensive radiation occurs in the immediate area of the injection of the isotope. However, the material may not be taken up by the lymphatics and delivered to the regional lymph nodes, as has been demonstrated with gold. It is questionable whether a lymph gland packed with tumor cells would receive additional radioactive material of any kind.

TECHNIQUE OF INJECTION

The perineal approach to the prostate for carrying out interstitial radiation of the gland was found unsatisfactory because it does not permit adequate exposure of the prostate and the regional lymph nodes. However, it has been suggested that the prostate be injected from both approaches in order to obtain a more thorough distribution of the isotope. In three of the patients, metastatic masses 2 and 3 cm. in diameter were encountered. In only one was the mass removed. A biopsy was always taken of the involved nodes, and an attempt was made to thoroughly infiltrate all palpable nodes with the radioactive material.

It has been observed that in the smaller prostates the response has been better. Therefore, an increasingly larger amount of prostatic tissue has been removed transvesically before carrying out the injection, and the number of points of injection have also been increased.

After the bladder is opened a finger is placed in the rectum, making palpation of the prostate gland possible, to determine the local extension of the disease, the consistency and size of the prostate (weight in grams). It is on this basis that the amount of radioactive material to be injected is calculated. A second biopsy of the prostate is always obtained at this time, and a revision of the bladder neck is carried out when obstruction is present. Multiple 21 caliber spinal puncture needles are inserted transvesically into the substance of the prostate, seminal vesicles, periprostatic tissues, and involved regional lymph nodes. The use of multiple needles has the advantage of obtaining more even distribution of the material, and in addition the immediate knowledge of direct entrance into a blood vessel, thus avoiding introducing of the material into the blood stream. Following the placing of the needles, the finger is removed from the rectum, making two hands available for manipulating the syringe, a distinct and welcome

advantage. The radiologist is always in attendance to calculate and to prepare the material to be injected in each case. The solutions contain from 1 to 3 millicuries of chromic phosphate per cc. To the isotope there is added 100 TU of hyaluronidase in 1 cc of 1:1000 epinephrine. Approximately 0.3 to 0.5 millicuries are injected for each gram of tissue; the largest amount injected in any single case was 40 millicuries.

A special syringe has been designed which permits the use of disposable glass cartridges. The material is packaged in these cartridges and therefore the loading of each syringe at the operating table is unnecessary. This minimizes the danger of contamination of the operator and operating room equipment. The syringe is shielded by a plastic cover which is adequate to filter out the beta rays (fig. 2).

The bladder is closed and drainage is maintained by an indwelling urethral catheter for 5 days.

The first 28 patients with cancer of the prostate who have been treated with chromic phosphate (P^{32}) are presented. The patients chosen for treatment were considered in stage two of the disease. With two exceptions they had all received

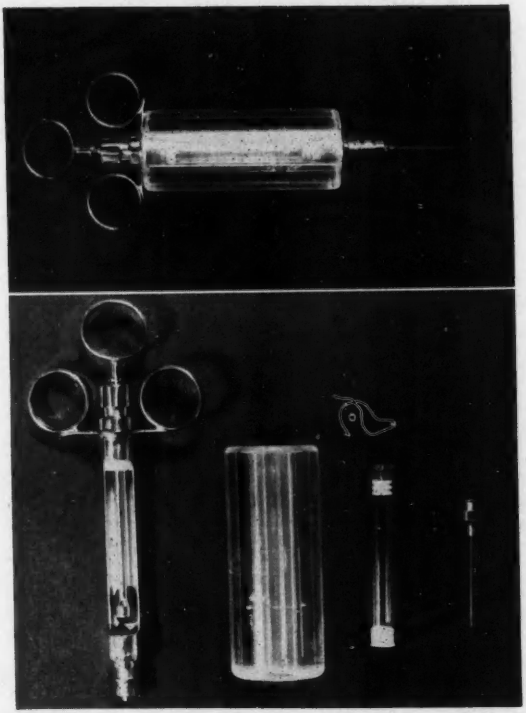


FIG. 2. Special syringe for injecting radioactive chromic phosphate into prostate. It is designed for use of disposable glass cartridges.

estrogens from six months to two years. Eight cases had bilateral orchiectomies prior to treatment.

RESULTS

Ages of patients, from 54 to 81.

Symptoms: Bladder neck obstruction, 8; acute retention, 13.

Previous surgery: Transurethral prostatic resection, 13; bilateral orchiectomy, 8; permanent suprapubic cystostomy, 2.

Unilateral or bilateral extension to the seminal vesicles: 28.

Acid phosphatase: Elevated in 6.

Amount of radioactive material introduced: 6 to 40 mc. chromic phosphate (P^{32}).

Number of deaths: 4. Cardiac arrest, 1; pulmonary embolus, 1; coronary, 2.

CLINICAL COURSE

Change in size of prostate: None in 10; decrease in 18. Change in consistency of prostate: Softening, 4; firmer, 14. Postoperative biopsies: 3 months, 10; 12 months, 1.

Although sufficient time for detailed evaluation has not elapsed, the clinical results of treatment in this small group of cases have been interesting and encouraging. In 14 cases there was a remarkable decrease in the size of the gland and a definite change in consistency of the prostate within 30 to 60 days following treatment. In 15 of the cases there was a gain in weight and a general feeling of well-being. In 2 patients osseous metastases developed following treatment, one at 6 months, and the other at 4 months, respectively. The microscopic findings are neither as striking nor as encouraging as the rectal and clinical findings. A biopsy with the perineal needle or transurethrally was obtained in all cases before treatment. A second was obtained transvesically at the time of injection of the isotope, and a third three to four months postoperatively. Tissue removed at 3 months was radioactive. Only ten of our patients have been treated more than 6 months, therefore postoperative biopsies have not been obtained in the other eighteen. In only one other case was a biopsy taken at 6 months. There was evidence of tumor in all biopsies. After a study of many sections in each patient, it was evident that there are histological changes in the radiated tissue when compared to the specimen of tumor obtained before treatment. Some sections revealed the presence of diffuse fibrosis and areas of necrosis. The nuclei of the malignant cells appear hypochromatic, irregular and shrunken, consistent with dying cells. However, in other areas in the same sections the tumor cells appear healthy and apparently are growing actively. The patient who has survived more than twelve months is in excellent general health, without evidence of metastases. The prostate is small, firm, and fixed. The sections of tissue removed prior to treatment show epithelial cells arranged in strands, columns with small acini. Diagnosis, adenocarcinoma (fig. 3, *A*). Sections of tissue obtained at 3 and 6 months after interstitial radiation with chromic phosphate showed many areas of increased fibrosis, with areas of necrosis and inflammation. At 12 months there was extensive fibrosis throughout areas of the sections, and large

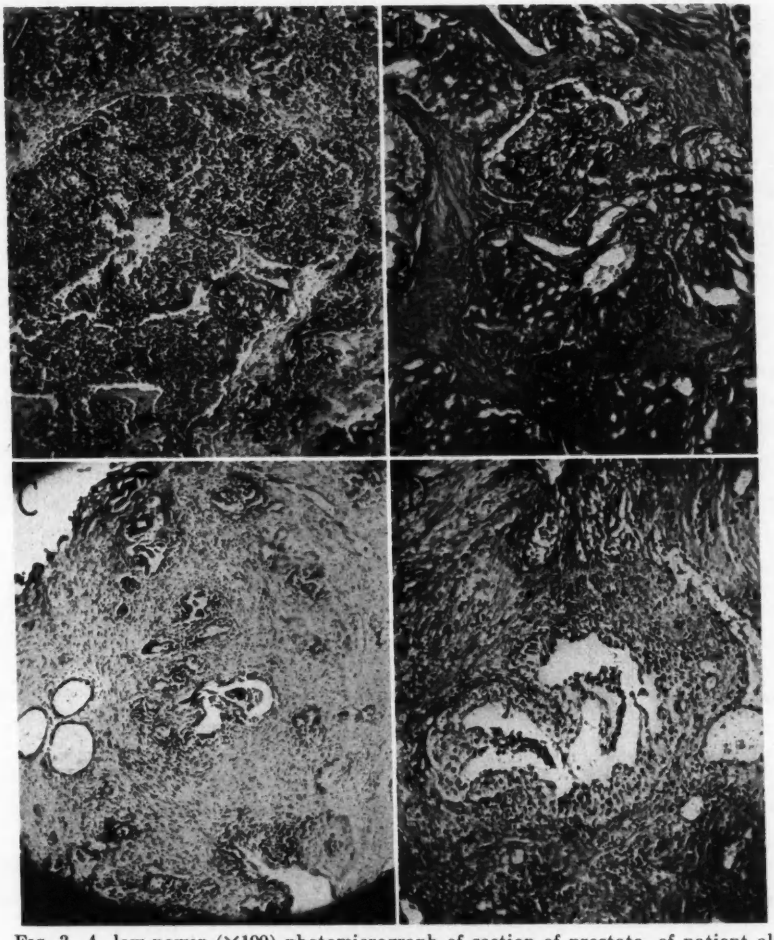


FIG. 3. *A*, low power (×100) photomicrograph of section of prostate, of patient alive over twelve months, prior to treatment. *B*, photomicrograph of section of prostate, same patient, 3 months following treatment. *C*, low power photomicrograph of section of prostate, 12 months following treatment, showing marked fibrosis and atypical glandular formation. *D*, high power section reveals same advance radiation changes. However, there are cells present which can not be distinguished morphologically from tumor cells.

masses of tumor cells revealed radiation changes, but it is not possible to say from the histology that the tumor was destroyed in a single case (fig. 3, *B*, *C*, *D*).

The marked scarring, necrosis, and diffuse fibrosis with the cellular changes which have been observed close to the site of the implanted radioactive material both in man and animal suggest that with thorough dispersion of radioactive chromic phosphate (P^{32}) throughout the organ, destruction of prostatic cancer should be obtained.

COMPLICATIONS

There have been no serious complications thus far. Some of the patients with edema of the rectal wall have complained of bowel irritation. Mild bladder symptoms have occurred in nearly all patients. These discomforts have subsided within 30 to 40 days. Immediate blood studies revealed a very small amount of material present, but there have been no late changes demonstrated in either blood or bone marrow. One patient, who died of pulmonary embolus after 5 days, showed radioactivity in the prostate and the associated pelvic tissues. The liver was slightly radioactive. There was no evidence of radioactivity in the spleen, kidneys, or lungs.

SUMMARY

Preliminary experience with the treatment of 28 cases of carcinoma of the prostate using colloidal radioactive chromic phosphate has been reported. Interstitial radiation of cancer of the prostate in stage two of the disease, using radioactive isotopes emitting beta radiation, seems encouraging.

The authors wish to extend their gratitude to Mortimer E. Morton, Chief of Radioisotope Unit, Veterans Hospital, Long Beach, for his valued assistance.

REFERENCES

BARRINGER, B. S.: Prostate carcinoma. J. Urol., **33:** 616, 1935.

BOTTSFORD, T. W., WHEELER, H. B., NEWTON, B. A. AND JAQUES, W. E.: Hypoplasia of bone marrow associated with radioactive colloidal gold therapy. J.A.M.A., **151:** 788–791, 1953.

BUGBEE, H. G.: Experiences with radium in cancer of the prostate. J. Urol., **6:** 459, 1921.

BUMPUS, H. C., JR.: Radium in cancer of the prostate, a report of two hundred and seventeen cases. J.A.M.A., **78:** 1374, 1922.

DEMING, C. L.: Carcinoma of the prostate and seminal vesicles treated with radium. Surg. Gynec. & Obst., **34:** 99, 1922.

FLOCKS, R. H., KERR, H. D., ELKINS, H. B. AND CULP, D.: Carcinoma of prostate. J. Urol., **68:** 510–522, 1952.

FLOCKS, R. H.: Treatment of carcinoma of prostate. Trans. Southeastern Sec. of A.U.A., pp. 94–101, 1952.

FLOCKS, R. H., HARNESS, W. N., TUDOR, J. M. AND PRENDERGAST, L. J.: Carcinoma of prostate. J. Urol., **66:** 393, 1951.

GOLDBLATT, HARRY: Personal communication.

YOUNG, H. H.: Use of radium in cancer of the prostate and bladder. J.A.M.A., **68:** 1174, 1917.

YOUNG, H. H.: Technique of radium treatment of cancer of the prostate and seminal vesicles. Surg. Gynec. & Obst., **34:** 93, 1922.

YOUNG, H. H. AND DAVIS, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926.

YOUNG, H. H.: Radical cure of carcinoma of the prostate. Surg. Gynec. & Obst., **64:** 472, 1937.

INTRAPROSTATIC INJECTIONS OF RADIOACTIVE COLLOIDS: II. DISTRIBUTION WITHIN THE PROSTATE AND TISSUE CHANGES FOLLOWING INJECTION IN THE DOG

GEORGE J. BULKLEY, JOHN A. COOPER* AND VINCENT J. O'CONOR

From the Departments of Urology and Biochemistry of Northwestern University Medical School, Chicago, Ill.

The recent availability of radioactive materials has led the urologist to search for substances which would be effective in destroying or controlling neoplasms of the prostate gland and bladder.

Radioactive colloidal gold injections, as a therapeutic measure have been advocated by Flocks and Kerr.[1] Their preliminary reports offer sufficient encouragement to prompt further and more extensive investigation.

After inspecting some of the clinical work of Dr. Flocks at Iowa City, we felt that additional experimental work, using dogs, might be helpful in clarifying some of the unanswered aspects of this problem. Two phases of the problem seemed important. Since we were unable to find any published reports detailing the distribution and excretion of the radiocolloids following injection into the prostate gland, we felt it would be worth while to undertake such studies in dogs. The detailed findings of this study have been made the subject of another preliminary report.[2]

The present report is an attempt to record exactly what occurs locally in the prostatic tissue as well as in distant organs of the dog after injections of radiocolloids. Early and late tissue changes as well as distribution of the material within the prostatic capsule have been studied. Additional observations will be reported after a still longer period has elapsed.

Radioactive colloidal chromic phosphate (P^{32}) was used in these studies as well as radioactive colloidal gold (Au 198), since we felt that radioactive phosphorus offered several theoretical advantages.

Radiophosphorus, which has a half-life of 14.3 days and emits only beta particles with maximum energy of 1.7 m.e.v., has many advantages over radiogold which has a half-life of 2.7 days and emits 0.95 m.e.v. beta rays and 0.74 m.e.v. gamma rays. The absence of gamma rays makes the handling of radiophosphorus simpler and the radiological hazard to the personnel less. The longer half-life and higher energy of the beta rays of radioactive phosphorus result in a more prolonged and greater radiation than can be achieved with radiogold, using an equal concentration per gram of tissue. Complete disintegration of one microcurie of P^{32} per gram of tissue will deliver a radiation dose of 885 equivalent

Work made possible by the Urologic Research Fund of Wesley Memorial Hospital and aided in part by funds supplied on Contract AT (11-1) 94 between Northwestern University and the U. S. Atomic Energy Commission.

* Markle Scholar in Medical Science.

[1] Flocks, R. H. and Kerr, H. D.: J. Urol., **68:** 510–522, 1952.

[2] Cooper, J. A. D., Bulkley, G. J. and O'Conor, V. J.: Intraprostatic injection of radioactive colloids: I. Distribution and excretion following injection in the dog. J. Urol., **71:** 624, 1954.

TABLE 1. *Comparison of radiation delivered by radioactive phosphorus and radioactive gold*

	FRACTION OF DECAY IN FIRST 24 HOURS	EQUIV. ROENTGENS DELIVERED IN FIRST 24 HOURS*	TOTAL EQUIV. ROENTGENS DELIVERED*
Au 198	0.23	19.3	84
P 32	0.047	41.6	885

* These figures are calculated for a dose of 1 microcurie per gram of tissue to complete disintegration.

roentgens (e.r.), while the same amount of Au 198 will deliver only 76 e.r. of beta radiation. The gamma ray contribution from gold is difficult to assess with certainty, but is of the order of 8 r per microcurie disintegrating[3] per gram of tissue. Thus, it is possible to deliver approximately ten times the radiation dosage with radioactive phosphorus as compared with radioactive gold. The range of the beta particles from radiophosphorus is about double that of radiogold. The longer half-life of P^{32} permits a longer period of storage before use.

The advantages of gold lie in whatever contribution the gamma radiation has to wider radiation of tissue. For large doses of radiogold, the roentgens delivered to the gland by gamma rays alone may be in the cancericidal range. This is important, if homogenous distribution in the gland cannot be achieved, since the effect of beta radiation is limited to a small volume surrounding the colloid. The apparent greater uniformity and stability of the gold colloid and the lesser tendency to form larger aggregates may also be advantageous. See table 1.

METHODS

Ten dogs were injected with colloidal chromic phosphate and nine with colloidal gold. The methods of injection and preparation of material are described in detail elsewhere.[2] Animals were sacrificed at intervals of two weeks to three months in the case of phosphorus, and intervals of one week to seven weeks in the case of gold. All organs were examined carefully both grossly and microscopically. Tissues were prepared in the usual way, using paraffin embedding for sectioning and were stained with hematoxylin and eosin. Fat stains were also done on the livers to detect possible liver damage. The prostates injected with gold were also stained by the method of Elftman and Elftman[4] to better visualize the colloidal particles of this material. Serial sections of the prostates were made in order to determine the distribution of colloid in all areas of the gland. See figure 1.

[3] Marinelli, L. O., Quinby, E. H. and Hine, G. J.: Dosage determination with radioactive isotopes: II. Practical considerations in therapy and protection. Am. J. of Roent. Rad. Therapy, **59:** 260, 1948.

[4] Elftman, H. and Elftman, A. G.: Histologic methods for the demonstration of gold in tissues. Stain Technol., **20:** 59–62, 1945.

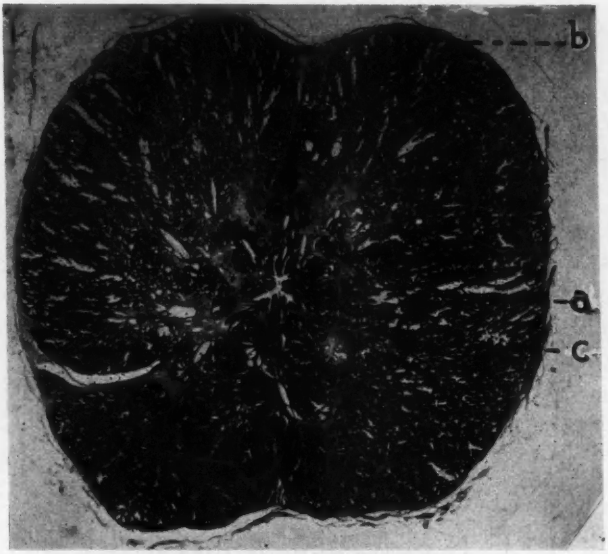


FIG. 1. Normal dog prostate

RESULTS

A. Radioactive colloidal chromic phosphate (P^{32}). The animals in this group showed no abnormal gross or microscopic findings except those to be described in the prostate gland and its investing layers. The regional lymph nodes were grossly unchanged and showed little, if any, radiation reaction.

There were a moderate number of periprostatic adhesions, more marked in the animals that had had extravasation of the radiogold at the time of injection. All of these adhesions were filmy and easily broken up by the finger. The prostate, itself, showed areas of subcapsular hemorrhagic reaction at two to five weeks. Serial sections of the gland revealed that the material had not been distributed uniformly throughout the tissue as we had hoped it might be, but that large areas of the gland were completely free of change. This was true in all of the prostates examined in spite of efforts to reach every part of the gland by the injecting needle.

Microscopically (figs. 2, 3 and 4), the reaction to radiophosphorus was marked first by acute necrosis, moderate hemorrhage and slight exudative reaction. The necrosis involved both fibrous and connective tissue as well as epithelial elements. The vessels showed a proliferative intimal arteritis with necrosis of the wall. This acute radiation reaction was very effective in destroying tissue, but it was even more apparent microscopically that much of the normal prostatic tissue remained unchanged. The acute reaction subsided after five to six weeks and healing became apparent at this time, and was fairly complete at the end

FIG. 2. Dog No. 1, five weeks after injection. Acute necrosis and hemorrhage following injection of radioactive phosphorus. Note incomplete distribution.

of three months. Healing by scar formation gave the picture of increased connective tissue, decreased or absent glands, pigmentation, cystic dilatation of nearby glands, and, in some areas, hyalinization. We were able to find normal glands in the center of an area of hyalinization in several cases, indicating that destruction had not been complete even in the center of the most marked radiation reaction.

B. Radioactive colloidal gold (Au 198). The animals in this group showed a much more marked periprostatic reaction as well as evidence of radiation effect in the regional lymph nodes. The dogs sacrificed at one and two weeks showed considerable edema of the periprostatic fat and enlarged hemorrhagic iliac lymph nodes. Those sacrificed at four and seven weeks had firm fibrous adhesions to the prostate and the gland was removed with difficulty for this reason. The lymph node change was quite prominent in this group. In the dogs injected with radiophosphorus, we had difficulty at autopsy in finding suitable regional nodes

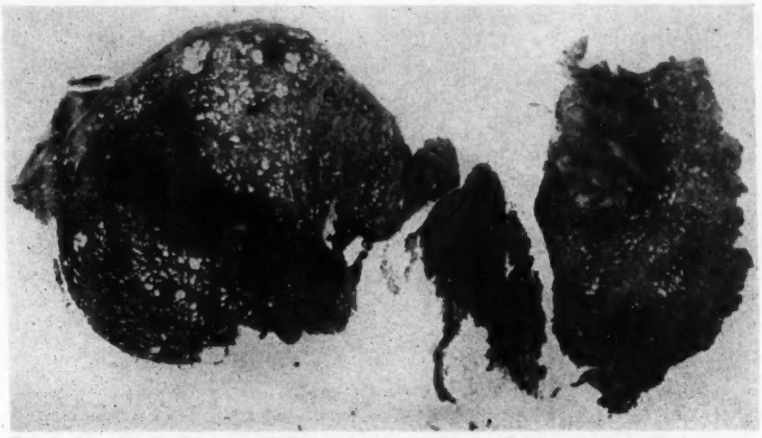


FIG. 3. Dog No. 6, two weeks after injection. Section showing acute radiation reaction to P 32 in a definite path through center of gland.

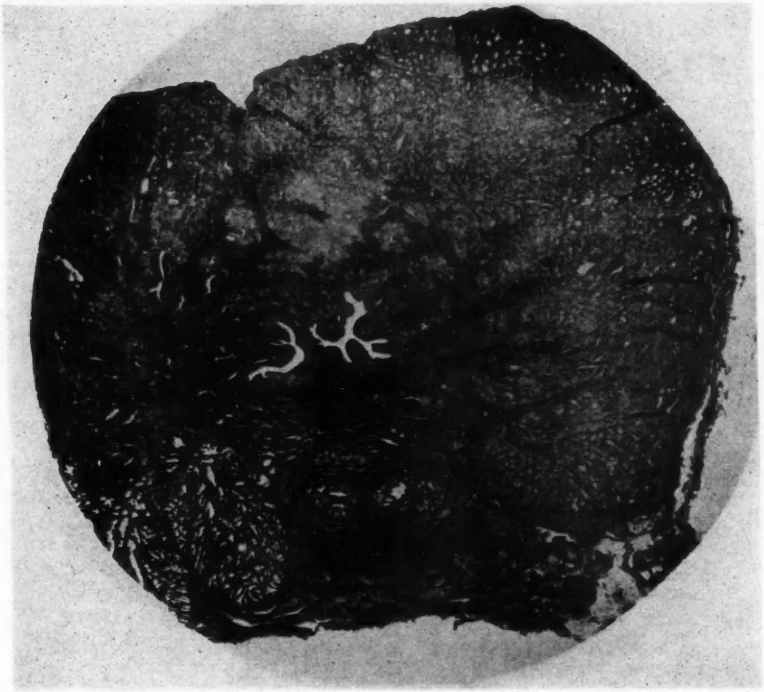


FIG. 4. Dog. No. 3, three months after injection of P 32. Section to show healed lesion with hyalinization and fibrosis. Note normal prostatic glands still present.

of any size for section, but, in the dogs injected with radiogold, these lymph nodes were enlarged two to three times, and, in most cases, hemorrhagic. Serial sections of the prostate, itself, showed a more marked capsular reaction, but about the same patchy pattern of distribution as we had observed in the case of radioactive phosphorus.

Microscopically (figs. 5 and 6), the acute reaction to radioactive gold was quite different from that observed in the previous group. Sections of prostates removed at one and two weeks showed an acute suppurative reaction with exudate in the glands and connective tissue. There were only small areas of hemorrhage and

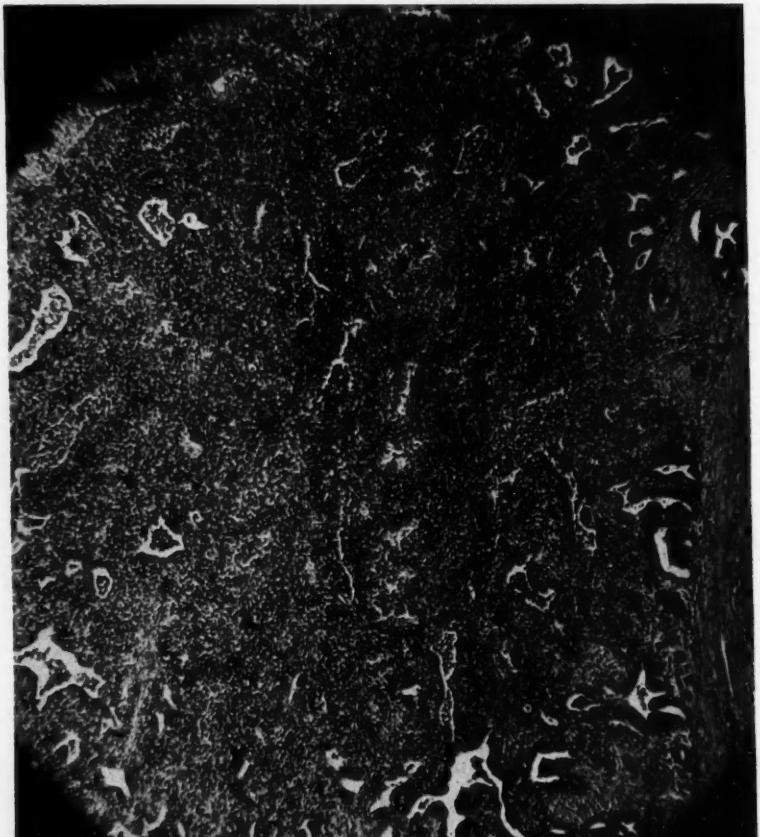


FIG. 5. Dog. No. 14, one month following injection of Au 198. Section to show acute radiation reaction resulting from injection of radioactive gold. Note exudative type reaction as contrasted with figure 2.

FIG. 6. Dog No. 13, seven weeks following injection of radioactive gold. Section to show late result following injection of radioactive gold. Area of scar surrounded by normal prostatic gland.

necrosis. The peritoneal reaction was more marked. The entire picture was that of an acute exudative reaction, and, at first, we thought we were dealing with a bacterial prostatitis. However, this suppurative type of reaction was a constant finding in all the five animals sacrificed at one and two weeks, and we feel that it represents the radiation reaction to the radioactive colloidal gold. Later results, microscopically, were very similar to those observed with phosphorus. Healing took place by scar formation with an increase in connective tissue which replaced the glands destroyed. Again we were able to find normal glands in the midst of this scar tissue, indicating that the radiation effect had

not been sufficient to destroy all of the prostatic glands, even where one would expect a maximum effect.

The liver and spleen showed no microscopic change in spite of the pickup of considerable radioactive material.[2] Other tissues were also unchanged grossly and microscopically.

DISCUSSION

It became apparent early in this study that our main problem was to achieve equal and uniform distribution of the colloidal material throughout the prostate gland. In the case of both radioactive gold and phosphorus, there was found to be little diffusion away from the path of the needle in spite of the addition of relatively large amounts of hyaluronidase and attempts to improve the technique by moving the needle to all sections of the gland. The material in many cases had apparently diffused out into the subcapsular space so that we found a marked capsular radiation reaction and periprostatitis, but many areas of prostate entirely free of change. Since many of the prostates weighed only five to ten grams, and were easily accessible at the time of injection, we had expected to achieve a fairly complete destruction of the entire prostate. We estimated roughly that we had destroyed as little as 15 per cent of the total prostate gland in some animals and as much as 75 per cent in others, but in none of these animals had we achieved complete destruction of tissue within the prostatic capsule. Flocks,[1] in his report on radioactive gold injected into human prostatic carcinoma, apparently experienced similar difficulties in distribution which he mentions in this report. This lack of distribution in the human is also borne out by the fact that he has been able to show radiation effects in only about half of the biopsies made after injection of radiogold into prostatic carcinoma.[5] It would seem from our studies on the dog that further efforts should be made to improve the technique of injection or the composition of the material, in order to insure a more complete distribution of the colloidal particles throughout the gland.

The lack of demonstrable damage to liver, spleen or other organs, in spite of relatively large pickup of radioactive material,[2] would seem to indicate that the materials are safe to use locally without fear of serious side effects. If a method can be devised to keep more of the radioactive material within the prostatic capsule, the possibility of damage to distant organs will be even less.

The lymph node changes, both grossly and microscopically, were quite prominent with radioactive gold, and this may be a definite advantage to the use of gold in cases of carcinoma of the human prostate with lymphatic spread. Little radiation change in the regional lymphatics was observed in the case of animals injected with radioactive phosphorus. These observations were borne out by the findings of much greater radioactivity in regional lymph nodes of animals injected with radiogold.[2]

The difference between the acute radiation effects of the two materials was quite striking. Radioactive chromic phosphate caused an acute necrosis and

[5] Flocks, R. H.: Personal communication.

hemorrhagic reaction with little exudative reaction. Radioactive gold, on the other hand, caused an acute exudative reaction with little necrosis or hemorrhage. This difference is difficult to explain. The late reaction of tissue to the two materials was quite similar.

CONCLUSIONS

The injection of radioactive colloidal chromic phosphate (P^{32}) and radioactive colloidal gold (Au 198) into the prostate of the dog causes no appreciable radiation effect in organs distant from the prostate. The only exception to this statement occurred in the case of the regional lymphatics following the injection of radiogold.

Distribution of the colloidal material throughout the prostate was not uniform in any instance, and in none of these animals was destruction of the normal prostate complete. Periprostatic reaction was marked in the case of both materials, but more prominent following the injection of radioactive gold. When healing had occurred, large numbers of normal prostatic glands remained, and, in some cases, normal glands persisted within the center of the healed radiation scar. This was true following injection of both radioactive gold and radioactive chromic phosphate.

The acute radiation reaction occurring in the dog's prostate to radioactive phosphorus differs from that seen due to radioactive gold, but the long term result is about the same following injection of either material.

720 N. Michigan Ave., Chicago 11, Ill.

DISCUSSION

DR. EDGAR BURNS (New Orleans, La.): I would like to confine my remarks to prostatic carcinoma treated by radioactive materials. This problem is so extensive that it cannot possibly be covered adequately within the time allotted for the discussion.

During the past 21 months we have treated 27 patients with radioactive gold, 23 of whom had prostatic carcinoma and 4 bladder tumors. We have attempted to determine the distribution of material.

We first worked out a method which I am sure most of you have also used trying to see how widely the material is distributed in the local area by taking a picture of the pelvis 24 hours after the injection. Here (slide) is a picture of a patient who had received 75 millicuries. At the end of 24 hours you can see the dark area, representing the distribution that can be demonstrated roentgenographically.

(Slide) This is a roentgenogram of a patient who received 126 millicuries, and I think you can see a rather wide distribution according to the dark area there, going well up to at least the crest of the ileum, and also down well below the prostatic area. Of course, some of that may be from the radiation that is not actually in the tissues, but simply the effect of it in the area of the catheter drainage.

(Slide) And this is a roentgenogram of a patient who received 112 millicuries, so apparently the amount that is used does make a difference in the shadow obtained at the end of 24 hours.

We have been able to demonstrate .03 per cent of the total dose in the blood serum in the first 96 hours after injection. We have also been able to measure 8 per cent of the total dose in the urine during the first five days. After that there is not enough to justify continuing the study.

Our observations have been similar to those mentioned by Dr. Bulkley a moment ago with regard to the amount in the liver, spleen and bone marrow. We have had no patients in whom there was any evidence of clinical damage to the liver, and I doubt, somewhat, you would. Certainly, if not more than .03 per cent reaches the blood serum, no particular damage in that direction would be expected.

I question somewhat whether there is enough concentration in the lymphatics to be of any importance in killing cancer cells.

The thing that has concerned us more than anything else is the amount of rectal irritation following the injection of radioactive gold. We have varied the site of injection in an attempt to prevent this.

We began to notice rectal irritation rather early in the series, and later, rectal slough. Of the 27 patients we have treated, complete slough of the rectum has occurred in 7.

This is important. If one could be perfectly certain that radioactive gold would cure the carcinoma, it would seem justifiable to sacrifice the rectum, as is done in rectal carcinoma, but so far we are not certain that a cure can be obtained.

We have attempted to explain the reason for the rectal reactions, the incidence of which, in our small series, seems to be greater than that reported by others, if we are getting the true picture.

We vary the site of injection. In the beginning we injected the seminal vesicles in all cases. Then we stopped injecting the seminal vesicles unless they were obviously involved. Now we give a more superficial injection into the prostate.

If the injection of carcinomatous areas must be avoided in order to prevent reactions, then the procedure would not seem to be a very good scientific one. In other words, if the growth of cancer is to be arrested treatment must be directed toward the involved area. That has concerned us a great deal.

In none of the patients in our series who have had complete slough of the rectum has the carcinoma been cured. In these cases biopsies have been performed at three-month intervals. In some of these patients the results of biopsy were negative at 3 months, in a few at 6 months, and they were positive in all at 9 months. Twenty per cent showed negative results at the end of the first 3 months, and then they gradually began to come back, and now in all those in whom biopsy was done at the end of 9 months, the results are positive.

It is certainly not my intention to be unenthusiastic about the use of radioactive material in the treatment of carcinoma of the prostate and bladder, but I do believe that we have to remember, always, what we are doing, in the use of any new material, and also where we are attempting to go.

Now, I would like to have one moment, if I may, Mr. Chairman, to say something about the 4 cases of bladder tumor. In one of them I am perfectly certain that we exploded cells into the circulation with the force that was necessary to try to infiltrate the tumor uniformly, because the patient had literally hundreds of cutaneous metastases. A biopsy from these cutaneous metastatic lesions revealed cells indistinguishable from those obtained by the original biopsy of the bladder tumor. I wondered if that same thing could not happen when the prostate is injected. You who have injected the prostate with radioactive substances know how difficult it is, and how much force is necessary to infiltrate the densely involved areas uniformly. I wonder if it is not possible—in doing that—to explode some of the cells into the circulation with resultant widespread metastases from the procedure.

I believe the effort should be continued, because we are dealing with an otherwise incurable disease, and if it can be cured by this method, of course, I think it is a justifiable procedure to continue, but at the same time we are deeply conscious of many of the things that may radiate from it. Thank you very much.

Dr. William P. Herbst, Jr. (Washington, D. C.): It seems to me that as we attempt to visualize and comprehend metabolically what goes on, clinically, we often experience periods of depression, frustration, and sometimes enthusiasm. I think Dr. Scott very aptly described the attitude of those who are most interested in the chemical metabolic research aspects of the problem when he said that if he didn't believe in it, he wouldn't persist in it.

I would like to comment on the clinical aspects of the problem in so far as life expectancy is concerned.

As of now, following a telephone conversation with Dr. Charles Huggins, concerning his first ten cases of castration, he told me there were still two out of the first 20 patients alive. In my own experience and follow-up of my other cases, I have only one alive—going on twelve years—so our actual ability to estimate accurately the life expectancy is not really possible at this time.

Dr. Scott may have mentioned a factor which he has thrown into the picture (I didn't hear him, but I have heard him speak about it several times before); namely, the prolactin relationship to androgenation. Dr. Scott has demonstrated the fact that androgen without prolactin—which is one of the pituitary secretions—is not effective so far as the specific influence on genital tissue is concerned, and that brings up, theoretically, the possibility of considering elaborating an anti-prolactin substance, and maybe treating some of these problems indirectly in that way.

There is another contribution which he made, involving the fact that the androgens are metabolized in the liver. In dogs they ran the blood from the left adrenal through the splenic vein, into the liver, and found that the androgens were removed.

I see, according to the press, that a surgeon in San Francisco did that a week ago on a human. It may be that this may be complicating our clinical procedures further.

Now, as to the time of institution of therapy. Having lived with these patients for nearly 13 years has resulted in a rather firm conviction and policy on my part—namely, that I do not and will not institute therapy until, if and when the patient is suffering from pain or has definitely unsatisfactory clinical trends. I feel justified in that, in view of the fact that I have patients I am following who are walking around and apparently are in good health, with extensive carcinoma of the prostate, with no symptoms. I resect them if they become obstructed.

When we do treat them, if we see fit to use estrogens, we use the smallest possible effective dose, and I haven't changed my mind about that, either.

In so far as the steroid pattern picture is concerned, some contributions are being made in identifying and analyzing quantitatively the steroids in the blood at the present time, and apparently they are finding some new steroids which we haven't identified before.

Calver, at the Naval Medical Center in Washington, is engaged in this work now, and he tells me that there is work being done in Worcester, Mass. along these same lines.

In so far as steroids are concerned, until we have the opportunity to see the clinical response when we see fit to use any steroid, we do not know what the potentialities are. If you will recall, the experimentation with cortisone that way was almost accidental, and we would never have known what cortisone would do if it hadn't been that they took a shot in the dark with the thing. They tried Compound A and had no response, and then, fortunately, they were able to get cortisone, and they used that, in large doses, and the experience there was good. Until we try these steroids, we do not know what they are going to do.

The relationship between steroids and enzymes is another interesting thing. It

is hard to say whether the enzymes influence the steroids or whether the steroids influence the enzymes. I rather have the feeling that they influence each other.

(Slide) These slides are made from data which I got from Dr. West, who has been associated with Dr. Carl Rusche in observations on chymotrypsin and rennin levels of patients under therapy who have prostatic malignancies.

As you see, this happens to be a patient with carcinoma of the prostate, showing that there was no response following thyroidectomy. The red line indicates the chymotrypsin inhibitor concentration, and the blue line the rennin inhibitor.

(Slide) Here we have two rather interesting graphs which he has produced.

The first one shows a case of carcinoma of the prostate, stimulated by just one dose of testosterone, demonstrating the extreme reaction to it.

Here is the point of injection of the testosterone, and you see this very rapid and marked response in the chymotrypsin level.

This is one of these paradoxical things which it is very difficult to understand or to satisfy ourselves about, chemically or theoretically. This is a case of carcinoma of the prostate with a long control—over two years—by the administration of testosterone.

Dr. Scott favors treating patients with testosterone.

In June 1950, the patient was on stilbestrol; then in August 1950, testosterone was started, first at the rate of 25 mg. a day, then 25 mg. every 2 days, and then 25 mg. 3 times weekly.

In 1952, from this figure here, you can see this progressively satisfactory trend in so far as the chymotrypsin level is concerned.

I have had no experience with this, personally, but it just seemed to me that this was so interesting that you would like to know about it.

There are other fields in this research activity, including psychochemical study pictures. I think that over this period of observation we have learned that it is impossible, clinically, to predict what will happen to any patient whom we see fit to treat in any way until we institute treatment, and we have to individualize with each patient in every respect as we go along. There is no such thing as routine and that seems to me to be the greatest lesson that we have learned from all these observations.

Another point is that we should maintain an optimistic attitude. Those who are working in the research field should continue in that field, and give us additional data as we go along, so that in the future—and probably not in the too distant future—we will have additional chemical armamentaria.

Again, those who are interested in the metabolic field cannot narrow their interests to the problems involving prostatic malignancy. Whenever you are interested in any metabolic field, you have to be interested in metabolism generally and broadly, because there is no such thing as a detachment or isolation in the metabolic field in so far as the research men are concerned.

Dr. Louis Orr (Orlando, Fla.): I would like to discuss briefly some of the problems relating to radiation with particular reference to radioisotopes, and also some of the mechanical features of the actual placement of these radioisotopes in tissue.

First, in a more or less informal fashion, I should like to say a word about chromic phosphate.

Phosphorus, or P^{32}, you will recall, is a beta-emitter and a high beta-emitter. Its gamma-emission is quite low. Gold 198 is a high gamma-emitter. The dispersion or diffusion of radiation from beta rays extends only a millimeter or so from the site of injection, which is the limit of the actual effect of radiation. In gamma radiation, as in gold, you have dissemination of gamma reaction at some distance from the limit at which the deposit is made. In other words, if you put a single radon seed into a mass you would have gamma radiation for a distance of ½ cm. on either side of the seed.

Up to this time we have had no difficulty with irritation of the rectum after the use of radioactive gold, as was true in Flocks's initial cases. Some of his early patients necessitated colostomies because of rectal slough and it is felt that he was probably placing the colloid too near the rectal mucosa, and they were suffering from the effects of high beta radiation. Beta radiation is extremely potent and will destroy any tissue in which it is placed. Of course, gamma radiation will do the same if it is placed close enough. It seems to me that the replacement of the radioactive colloid so that it may deliver a high gamma element into an area not too close to the rectal mucosa would be the ideal way of treating advanced cancer of the prostate.

Although we have just recently begun work with humans, it is our initial feeling, and has been for a period of 18 months of close study, that probably the best distribution of radioactive gold into the prostate will have to be a combined operation of retropublic and perineal insertion. Flocks has fairly well established the dosage and also relative measurements for mass related to dosage. In other words, a malignant mass the size of a lemon will represent between 90 and 110 grams of prostatic tissue. We have increased our dosage from two to three millicuries as was used originally, to five millicuries per cubic centimeter. The dosage as we would compute it, based upon Flocks's findings, would be about one millicurie per gram of malignant mass.

Some eighteen months ago I was discouraged by Brucer of Oak Ridge about trying to do any experimental work on the degree of radiation diffusion in experimental animals. In placing radiation material into the carcinomatous mass you are dealing with almost solid material and the diffusion pattern is different from that found in the normal tissues. There has been nothing but trial and error as a base upon which to regulate dosage and distribution.

We shall strive, as are others who are using radioactive isotopes, to develop the best plan whereby a high gamma emitter can be more accurately placed in the periphery of the prostate and also in the fascial compartments containing the seminal vesicles.

Although gold is the element now in use, no doubt there will be hundreds of other elements in the future which will be proved to be even better emitters of radiation than gold. I might call attention to the fact that Letecium is an element which offers great possibilities because of the uniformity of its particles, which has much to do with the delivery of radioactivity. Unfortunately, chromic

phosphate does not have a uniform pattern. Letecium is much cheaper to produce and is a better gamma emitter than gold or any other element being utilized at this time.

In Flocks's clinic it has been found that masses of cancerous cells have been left in the prostate along the walls of the urethra. This of course, is due to the difficult disposition and radioactive materials in this area.

Transurethral resections have been done following the use of gold and have proved conclusively that islands of nonaffected tissue have been left in certain portions of the mid-section of the prostate along the urethra.

An interesting piece of work has just been done by Berg of Louisville, who recently read a paper on radiation uptake at the 1953 meeting of the Southeastern Section in Havana. This work showed that by injecting Au 198 into the dome of the bladder the radiation uptake was highest in the region of the trigone. Of course, this is where most of our tumors occur and this, no doubt, will prove itself to be an important contribution as time goes on.

I should like to ask a question regarding the distribution of chromic phosphate in the cancerous prostate. We have a partial answer to this problem by post-mortem examination and also tissue removal following injection when gold has been used, but I do not believe that any similarity can be drawn by the chromic phosphate distribution in the normal dog and that in cancerous tissue.

It seems to me that all of this work with the isotopes should be looked at from a very conservative viewpoint and the approach should be most careful and judicious before any basic statements or claims of arrest or cure can be made.

One other problem upon which we have been doing considerable work, as have been the British, is the vexing problem of multiple papillomatosis of the bladder. It is conceivable that if a good beta-emitter could be delivered through some substance to the surface of the bladder, it would not be at all impossible to destroy multiple papillomas, or certainly to retard the development of these very annoying growths.

The technical difficulty has been in the development of a balloon similar to this I wish to show you. This is a crude specimen but it is a balloon catheter with a longitudinal partition. Into either or both of these compartments could be injected a radioisotope, and if a satisfactory beta-emitter could be put into one side and applied next to the bladder wall, it seems not unlikely that some therapeutic value might be gained by such a procedure. Maynard of England has had the same idea in mind but has not been able to develop the catheter which has been done by an American manufacturer. Dr. Brucer, of Oak Ridge, is going over in June to discuss the whole situation, and perhaps from what can be gained from their conference some progress in delivering this type of radiotherapy to the bladder wall can be gained.

I would like to show three slides to illustrate some of the things we have been doing to overcome the mechanical difficulty in delivering radioactive gold to prostatic cancer.

(Slide) This is a method of filling which is rather ingenious. This is the gold 198 in the container; here is an air syringe full of air with plastic tubing. This can

deliver an air column down to the bottom of this vial. This is delivered through the catheter which is, incidentally, a number 8 ureteral catheter, which we are now having made with lead rather than tin as its structural base. Tin is the ordinary element used to produce radio-opacity in a catheter. We are now having a larger catheter made filled with lead with a lumen the size of a 20 gauge needle. This material is delivered into the 30 cc syringe, which is completely lead covered.

(Slide) In preparing for the injection we have devised a lead covered needle about 6 inches long, which is approximately the size of a pencil, with the needle protruding from the end about ½ cm. to prevent too great depth of injection. Here is a lead box, which is entirely home made, but which covers an ordinary pentothal delivering apparatus, such as anesthetists use. A calibration is placed on the plunger so we can fairly accurately, even at this distance, deliver a 1 cc dose.

(Slide) Here is a breakdown which shows the needle and other parts of the equipment. Of course, you will ask—what is to keep the needles from coming off? They will be swaged on so that under pressure you will not be able to blow them off, even though the foot-pound pressure will be heavy in delivering the material into the cancerous tissue. From the standpoint of danger to the surgeon, you can hold this catheter in your hand for 15 minutes and not receive more than a few milliroentgens, which is a safe dosage if not used more than once a week. The great advantage to this equipment is that you can work at some distance from the radioactive substance and with the type needle here illustrated it will give you much more latitude in directing the injection of the material.

I have seen a number of Flocks's patients 7 to 10 months after their initial surgery and injection with gold and the results have been perfectly amazing. Two of my own patients, whom he treated some months ago, have gained 30 to 35 pounds each and there is no clinical evidence of cancer in either of these patients at this time, although they showed stony hard prostates before the operation.

All of this work is extremely interesting and I believe that if it is pursued with the required caution it may be that we can offer something to the patient with incurable prostatic cancer beyond the methods now utilized.

Dr. Vincent J. O'Conor (Chicago, Ill.): It is evident from this morning's program that the problem of prostatic cancer is still a major one. It is of interest to me in that we seem to be clarifying facts to show that it is not only a local disease, but a general one. That is the way I have always felt about it.

I have felt that way about it because of observations such as Dr. W. W. Scott enumerated here this morning. I have watched patients live for 18 years or longer with a proven cancer of the prostate with no treatment. Many of these patients die of some disease other than their cancer.

I have watched my own next-of-age brother for 9 years. He died 2 years ago from a coronary thrombosis, rather unexpectedly. He had a cancer of the prostate which had responded to estrogen therapy. He didn't know what he had. When he stopped estrogen therapy, his cancer would grow rapidly. At autopsy, the pathologist—a very good one—said that unless I had asked him to make serial sections of the prostate, he wouldn't have been able to tell that a carcinoma

existed. He then stated that it was an early carcinoma of the prostate, even though it had been diagnosed as such 9 years previously.

So, as Dr. Scott has so very definitely said, all prostatic cancers are certainly not alike from the point of view of malignancy.

In 1943, Dr. Robert McAllister (who is now in Macon) and I picked out 50 patients with carcinoma of the prostate for detailed study. I have been able to follow those 50 patients for the past ten years. Every one of them has been followed carefully and satisfactorily. Three of that group are still alive and are without evidence of exacerbation of their disease. All these men are in their late seventies. Two of them had metastases in the spine, which have healed following orchiectomy and estrogen therapy, that is, from an x-ray point of view.

We have tried to evaluate in a gross way what happened to the adrenals in these patients who had reactivation of the disease where they had previously had a fairly long period of androgen control therapy. We have autopsies on six of these patients who were followed over five years, who responded very well to estrogen or estrogen and castration; then the disease became reactivated, and they died of the cancer.

Grossly, there is no change in the adrenal glands, and, according to our pathologist, there has been no change in the texture of the gland itself, microscopically. From a point of view of the size, the weight of the ordinary microscopic picture of the adrenal, there is no evidence of reactivation from that point.

We ran 17 ketosteroids on 12 of these patients before their clinical reactivation was definite, and we ran them during the last days of their lives, when they were dying of cancer, and there is no appreciable difference in that small series in the 17 ketosteroid excretion tests as run by Dr. Smith Freeman in our biochemical laboratory at Northwestern.

At the present time, in accord with a request by Merrell & Company, who are interested in TACE, we are running frequent steroid determinations on 20 patients who are currently under control with their disease, and if we can follow these patients long enough, when their disease is reactivated, to run another comparative group of 17 ketosteroid excretions, we should be able to see if there is any increase which we have not found so far.

It is quite evident that our problem is both systemic and local in cancer of the prostate, and, naturally, this effort to eradicate the local cancer, whether it is by extirpation or by radiation, is only a part of the problem.

As far as injecting the prostate itself is concerned, we know from previous studies in dogs that we can create a fibrosis in the prostate of the dog by merely needling the gland. We can create a very good hyalinization of the normal prostate in the dog by injecting water, salt solution and, of course, the degree of fibrosis increases with the irritant activity of the material injected, such as mercurochrome or colloidal silver solution.

Actually, from a purely microscopic point of view, these prostates in dogs look quite similar to the prostates of dogs that Ladd and I injected ten, twelve or fifteen years ago with such substances as acriflavine and mercurochrome, and so forth. In other words, where we were able to stir up enough reaction in the gland,

we had an encroaching hyalinization or fibrosis which destroyed the glandular elements. However, as has been said, that should not deter us from going ahead with the radioisotopic work, because, as I think Louis Orr said, we certainly are on the doorstep of something that may enable us to deliver radiation therapy such as we have never been able to deliver to the tissue before.

With chromic phosphate, we can deliver, without destroying other tissues, about 90 times as much radiation as we could from external sources, so that when, as and if we could have some method where we could actually place this material in a satisfactory manner, we might be able to destroy the carcinoma locally. Now, whether destroying these carcinomas locally is going to cure the patient or not is another thing. I don't think that chromic phosphate or radioactive gold will be the answer to the local or systemic problem, but continued research along these lines is certainly indicated.

DR. W. W. SCOTT (Rochester, N. Y.): Along with Dr. William Scott I think many of us can recall the occasional patient with proven carcinoma of the prostate in whom the growth without the benefit of endocrine therapy remained relatively dormant for many years. But as pointed out by Dr. William Scott and Dr. O'Conor, we have no means of predicting in advance with any degree of accuracy the future course of the disease in any given case of carcinoma of the prostate. Because dormancy of growth seems to be more frequently observed in patients of advanced age, we have never performed the follow-up radical perineal prostatectomy in any patient who was 80 or more years of age when first seen.

It seems to me that such cases would appear with about the same degree of frequency in any comparative study of the results of various types of therapy such as presented in table 1, providing the number of cases in each category were sufficiently large to permit the relative sequence of their occurrence to be established. These cases must be quite uncommon. I doubt if any of us can recall more than two or three of them in our personal experience. Consequently such a case is more likely to be absent in a small group and therefore to affect adversely rather than favorably its relative therapeutic position. It was because our series is so small that we make no claims for it, except that the results to date seem to indicate that it is worthy of further trial.

Both of the discussants have placed great emphasis on the general aspects of this disease and rightly so, inasmuch as most of the patients are in that stage when first seen. However, I think we must not forget that at first this disease is confined to the prostate gland and in this stage is best treated by the radical removal of that organ. In combining the endocrine therapy with the follow-up radical perineal prostatectomy in selected cases of advanced carcinoma of the prostate gland which were without proven metastasis when first seen, we are but attempting to broaden the field of usefulness of this operative procedure. In 2 of our 5 failures to date, I believe we have lengthened the life of the patient and I know we have greatly increased the period of freedom from the distressing urinary symptoms that so frequently occur in the late stages of the disease.

I wish to take this opportunity to thank the discussants for their very pertinent remarks on this subject.

SCHWANNOMAS

CLYDE L. DEMING AND HARRY R. NEWMAN

From the Department of Surgery, Section on Urology, Yale University School of Medicine, and the Grace-New Haven Community Hospital, New Haven, Conn.

Schwannomas, or, as they are often called, neurinomas or perineural fibroblastomas, arise from the sheath of Schwann, usually from a peripheral nerve. The commonest nerve to be involved is the acoustic nerve.

In reviewing the literature, such a tumor in the retroperitoneal space in close association with the kidney and ureter has not been recorded. The commonest retroperitoneal tumors arising in this region have been reported by Donnelly and Judd. Whether schwannomas in this region have not been recognized or whether they have been confused with the more common tumors such as sarcomas, fibrosarcomas, neuroblastomas, sympathicoblastomas, sarcomas and cystic tumors one cannot proffer an excuse. Frank described a cystic schwannoma containing five or six ounces of clear fluid which arose from low down in the pelvis and had to be differentiated from an ovarian cystic tumor. So far as the literature is concerned, urologists have not before encountered schwannomas which produced urinary tract changes. The authors wish to report two cases of schwannoma, both in female adults, one a solid, relatively benign tumor and the other cystic, with a relatively high degree of malignancy.

CASE REPORTS

Case 1. A white woman, aged 31 (Mrs. E. D., Unit No. C 55562), was admitted to the Urological Service of the New Haven Hospital on April 12, 1951, complaining of a feeling of fullness in the epigastric region for a period of 1 month. She was in the third month of her second pregnancy. She denied any nausea, vomiting or urinary symptoms. She had never had any hematuria. Her family history was irrelevant, and her past history showed good health respective to all systems and one pregnancy which had terminated normally 19 months previously. The family history disclosed that her father died at 66 years of leukemia and asthma and that her mother had been operated upon for a myoma of the uterus. Her general condition was good. Physical examination revealed that the left side of the abdomen was larger than the right. A mass was palpable in the left flank extending from under the costal cage down to the crest of the ilium, smooth in contour, soft in consistency and not particularly tender. The pelvic examination was compatible with the stated pregnancy. Cystoscopic examination showed a normal bladder. The bladder urine was clear in color; pH, 5.5; specific gravity, 1.010; albumin, 0; sugar, 0; microscopic examination showed no pus cells or red blood cells. The urines from the right and left kidneys were normal. Cultures of the urine from each kidney and the bladder were negative for bacterial growth. The renal function test with phenolsulfonphthalein disclosed 25 per cent from the right kidney and 20 per cent from the left kidney in 15 minutes. Bilateral retrograde pyelograms (fig. 1) revealed a normal right kidney, pelvis and ureter. On the left,

FIG. 1. Case 1. Retrograde pyelogram showing left ureter taking lateral, curved course with dilatation of upper two-thirds. Slight dilatation of pelvis with delicate calyces and high position of kidney.

the ureter took a normal course up to the pelvic brim, swept laterally and posteriorly and returned to the left paravertebral region at the level of the first lumbar vertebra, where the ureter was moderately dilated between the pelvic brim and the renal pelvis. The major and minor calyces of the left kidney were outlined, showed no evidence of dilatation and were less filled than the calyces on the right. The lower and middle calyces were displaced upward and were crowded together as the result of displacement by a large, space-occupying lesion of the lower pole of the left kidney which also displaced the ureter posteriorly and laterally. This large, soft-tissue density showed smooth edges with regular outline and no evidence of calcification and was thought probably to represent an enlarged cyst of the lower pole of the left kidney. The chest x-ray revealed normal bony thorax, diaphragm, heart and mediastinal contents with clear lung fields. The differential diagnosis preoperatively was between 1) retroperitoneal tumor, 2) hydronephrosis of the lower half of the kidney and 3) solitary cyst of the kidney.

Treatment:—On April 17, 1951, the left flank was explored through a lumbar incision. A large tumor shaped like a football was located below the left kidney but not attached to the kidney. Its surface was smooth, solid in consistency and adherent to the posterior abdominal wall and to the descending aorta. The tumor was carefully dissected free and removed. There were not any lymph node involvements. The retroperitoneal space was drained with a cigarette Penrose drain. The patient was discharged from the hospital on the eleventh day after operation in excellent condition and with the wound completely healed.

The pathological report of the tumor (fig. 2) removed is as follows:

FIG. 2. Case 1. Cross section of solid schwannoma which is well encapsulated

"The tumor is lemon shaped, measuring 17 cm. by 13 cm.; total weight is 1680 gm. Its surface is covered by fascia which can be stripped from the tumor with only slight difficulty, leaving a shiny, yellow and gray glistening surface. The cut surface of the tumor is yellowish-gray in color, soft in consistency and cystic. The microscopic sections show connective tissue containing areas of dense bundles of fibrous-like cells with long, narrow, elongated blue nuclei (fig. 5, *A*). These bundles of tissue seem to interweave, and in some areas the nuclei give the impression of palisading. In other areas loose connective tissue is present. The connective tissue gives the general appearance of having been fatty tissue. In other areas of this connective tissue many round, blue-staining cells are seen which may be chronic inflammatory cells. A large number of small-sized blood vessels are also seen in the tissue. Pathological diagnosis: Schwannoma."

This patient made an uneventful recovery from the operation and 7 months later delivered a normal boy. Six weeks after the operation an excretory urogram revealed slight dilatation of both ureters and pelves, but otherwise the urinary tract was normal.

Case 2. A white woman, aged 33, was admitted to the Urological Service of the Grace-New Haven Community Hospital on November 7, 1948. Her complaints were numerous and varied. She complained of vague abdominal discomfort which was not associated with meals. She had bouts of bronchial asthma. Her

previous hospital admissions were numerous, and her symptoms were explained on the basis of allergy. Physical examination revealed this patient to have marked scoliosis and lordosis of the thoracic and lumbar vertebrae, a deformity which had been present since birth. Abdominal examination revealed a palpable mass in the left flank, smooth in contour and solid in consistency, which was thought to be a palpable left kidney as a result of displacement caused by the associated scoliosis. The bladder urine was normal, and microscopic examination showed no evidence of pus cells or red blood cells. The urine from each kidney was normal,

FIG. 3. Case 2. Retrograde pyelogram showing axial torsion of left kidney caused by mass located below kidney and medial deviation of course of ureter.

and the culture from each kidney was negative for bacterial growth. The function of each kidney as measured by the phenolsulfonphthalein test was within normal limits. Bilateral pyelo-ureterograms showed a marked axial torsion of the lower pole of the left kidney caused by a large, well-defined mass below the lower pole of the left kidney (fig. 3). The differential diagnosis was between a tumor of the lower pole of the kidney and a primary retroperitoneal tumor, extrarenal in origin.

Treatment:—At operation, a modified left kidney incision was made below and parallel to the twelfth rib and extending towards the umbilicus in a transverse direction. The retroperitoneal space was opened and a large tumor was located extending from the level of the lower pole of the kidney to the crest of the ilium. The tumor was the size of a grapefruit and seemed to be attached medially to the vertebral column. Anterior to it was found a large band of nerve tissue about half an inch in width. The tumor, which was solid in consistency and encapsulated, was excised conserving the kidney.

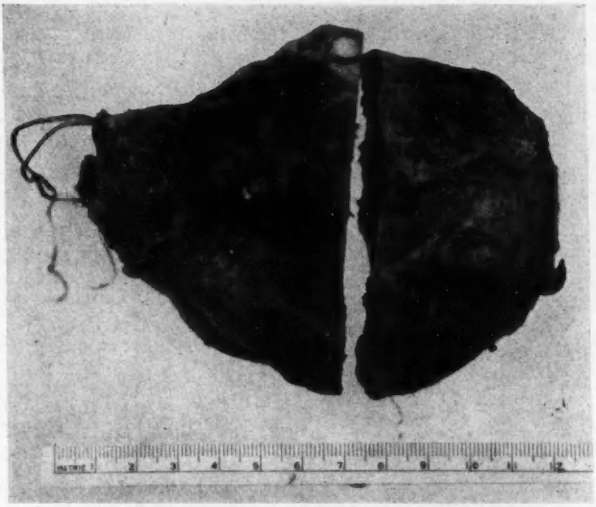


FIG. 4. Case 2. Thick-walled, cystic schwannoma

The pathological report is as follows:

"A thick-walled, cystic tumor (fig. 4), the size of a small grapefruit. The surface is roughly nodular. Cross section of the mass reveals it to be solid with a large area of degeneration and cyst formation. A large nerve trunk issues from one pole of the tumor mass. Microscopic pathological diagnosis: Cystic schwannoma of a retroperitoneal tumor." See figure 5, *B*.

The patient made an uneventful recovery from surgery and was discharged from the hospital 2 weeks later. Three months after the operation she had gained 13 pounds in weight. On July 5, 1949, eight months after surgery, she again began complaining of pain in the left flank accompanied by nausea. She was re-admitted to the hospital on August 18, 1949, complaining of more severe pain in the left upper quadrant of the abdomen accompanied by nausea and vomiting. She had also noted a localized swelling between the eighth and ninth ribs in the left anterior axillary line. Abdominal examination revealed in the left upper quadrant a firm mass measuring about 5 by 6 cm., which did not move with respiration. X-ray study of the chest revealed erosion of the anterior one-third of the left seventh rib at the anterior axillary line and extending from this ragged anterior margin of the seventh rib a large, soft-tissue mass measuring approximately 5 by 7 cm. in diameter. Excretory urograms revealed a normal right kidney, pelvis and ureter. There was no evidence of excretion of dye by the left kidney.

Cystoscopic examination was done, and both ureters were catheterized. Bilateral pyelograms showed failure of the left urinary tract to fill above the fifth lumbar vertebra where a soft-tissue mass could be seen to the left of the vertebral column at the level of the fourth and fifth lumbar vertebrae. The right kidney, pelvis and ureter were normal.

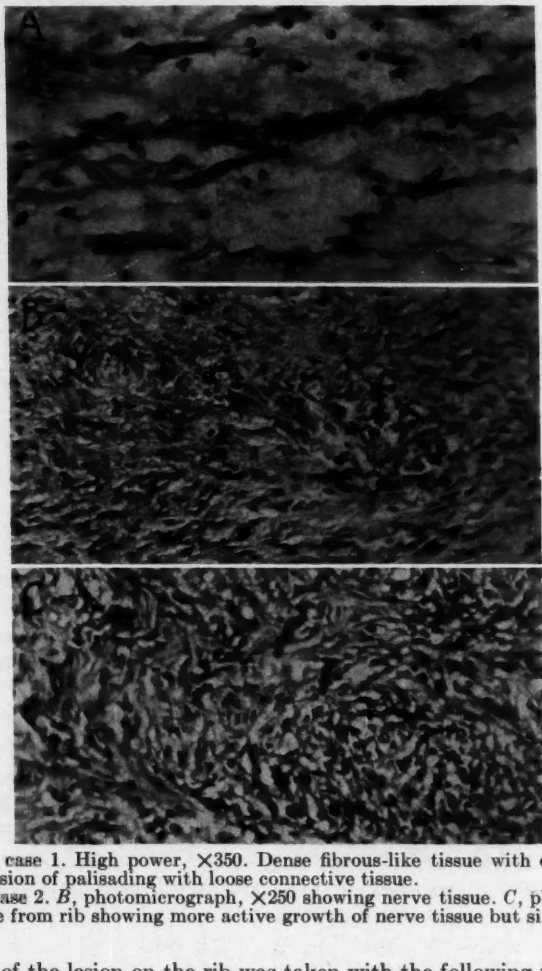


FIG. 5. *A*, case 1. High power, ×350. Dense fibrous-like tissue with elongated nuclei giving impression of palisading with loose connective tissue.
B and *C*, case 2. *B*, photomicrograph, ×250 showing nerve tissue. *C*, photomicrograph, ×250. Nodule from rib showing more active growth of nerve tissue but similar to original lesion.

A biopsy of the lesion on the rib was taken with the following report:

"The specimen consists of two pieces of firm, grayish-pink, gritty tissue each measuring approximately 1 cm. in diameter. Microscopic examination shows whorls of fibrous tissue arranged in irregular patterns. The nuclei of these fibroblasts vary greatly in size, shape and staining reaction and often are large, vesicular and with large nucleoli. A moderate number of mitotic figures are visualized. Diagnosis: Malignant schwannoma (Dr. Levin Waters)." See figure 5, *C*.

The patient expired on October 27, 1949.

PATHOLOGY

There are two types of schwannomas, the benign and the malignant schwannoma. Both of these types are associated with peripheral nerves and are ex-

tremely rare in the retroperitoneal space. The malignant schwannoma is often labelled a fibrosarcoma, but the origin of this tumor is different. In the main, the above two tumors arise from Schwann cells which have their embryonic origin, the neural crest. The Schwann cells are very active and multiply easily. Tissue cultures have shown that these cells can produce connective tissue fibers. Whenever a malignant tumor arises from the sheath of a peripheral nerve there crops up uncertainty in one's mind as to the embryonic origin of these cells. If this type of tumor arises from mesodermal connective tissue it is called a fibrosarcoma. It is uncertain whether or not the mesodermal element of a nerve sheath can produce a malignant fibrous tissue. The solitary, encapsulated, benign tumor which arises from the sheath of Schwann may be small, solid or large and cystic. The small tumors are solid, but as they grow larger degeneration occurs and cystic formation results. They grow slowly, usually without producing symptoms, although when a large nerve trunk is expanded, pain, paresthesia or other symptoms due to pressure may occur. The solid tumors are benign and are always encapsulated and rarely recur after surgical removal even if the capsule is left behind. It has been questionable whether or not a malignant tumor ever develops from them. Histologically, the microscopic picture is characteristic. Inside the sheath, the tumor tissue is composed of two parts. The cells of Schwann are arranged in twisted bands or cords accompanied by delicate connective tissue fibers. The cells may also be arranged so as to give the appearance of a tactile corpuscle, which is called a Verocay body. Del Rio Ortega, Penfield and Mason have divided the nerve tumors into two types, the fascialar and the reticular. The former consists of an orderly arrangement of parallel and intercel ular fibers. The cells may also present transverse parallel ranks separated by nuclear free zones of densely aggregate fibers along with the terminal portions of the cells. The neurilemmoma consist of a form of reticular collogen which, however, stains somewhat differently from the fibroblastic collogen. The reticular type shows a disorderly arrangement of a loose meshwork of cells of variable shapes with plentiful intercellular vacuoles or microcytes containing water or mucinoid fluid which stains bluish with benatoxylin. Regimented parallel fibers are not found and collogen fibers are scanty or absent in this type. The two types may be found together. Biologically, they grow slow and are encapsulated. If they are not entirely removed recurrence may develop.

COMMENT

These 2 cases of schwannomas occurred in young adult women and on the left sides. Both were operated upon successfully conserving the kidneys. One tumor was solid and relatively benign, and the other cystic and malignant. It is difficult to state how long these tumors had been present. The former had produced almost no symptoms while the latter had presented symptoms for 10 years. Schwannomas as a rule are relatively benign tumors, although the cystic ones may prove to be malignant. The former patient has remained well for two years, while the latter patient died of general metastatic lesions eighteen months from the time of the operation. Schwannomas are slow-growing tumors and rarely reach more than two centimeters in diameter. The schwannomas in the retroperi-

toneal space below the renal organ develop into large tumors which compress the ureter and influence its position and function. They are adherent to the posterior abdominal structures, both muscle and vascular tissues. Care should be taken to remove all of the tumor as in all tumor surgery. In the second case, it was more difficult to accomplish complete removal, and, as evidenced by its local recurrence, the tumor was not wholly removed. The widespread metastases indicate the true biological tendency in this one case of disseminating its growth to distant tissues. Neuropathological literature indicates that the tumors may become cystic and malignant, although on the whole they are considered relatively benign.

REFERENCES

DONNELLY, B. A.: Surg., Gynec. & Obst., **83:** 705, 1946.
FRANK, R. T.: Surgery, **4:** 562, 1938.
JUDD, E. S., AND LARSON, M.: Surg. Clin. North Amer., **12:** 823, 1933.
MILLER, J. R.: Am. J. Obst., **32:** 652, 1936.

DISCUSSION

Dr. Austin I. Dodson (Richmond, Va.): Dr. Deming's paper creates interest, so far as I am concerned, because of a patient who may come in this classification.

This was a six year old child, who was operated upon for the removal of a Wilms's tumor. The surgeon considered that it could not be removed. He sent the child to me with the hope that I might remove the tumor. In the meantime, the patient had received 900 roentgens of x-ray therapy. When the child came to me, there was a clearly palpable tumor in the left flank.

At operation, the tumor covered the aorta on two sides; it cupped over the aorta. The tumor was very intimately connected with or adherent to the lower part of the kidney, and the renal vein spread over the tumor and was unrecognized and injured, consequently the kidney was removed.

I do not recall the exact measurements of this growth, but it was a sizable tumor, probably as big as a small orange. It was larger than the child's kidney, which was of normal size for a six year old.

The growth was submitted to three pathologists. One called it a neuroma, one called it a neuroglioma, and another called it a benign tumor of unknown origin.

Dr. Clyde L. Deming (New Haven, Conn.): There may be more of these tumors. I think we should go over our pathological reports more carefully and definitely segregate them from the fibrosarcomas. Nerve stain and collagen stain would probably help us to make an accurate diagnosis in these cases.

ELECTROMYOGRAPHY OF THE URINARY BLADDER

SAMUEL A. VEST AND E. L. COREY

From the Departments of Urology and Physiology, University of Virginia Hospital, Charlottesville, Va.

The recording of bio-e ectric potentials from the musculature of the urinary bladder was initially attempted because of the recognized shortcomings of the conventional cystometrogram.[1, 2, 3] It was also hoped that such electromyographic evaluation might indicate the functional state of the viscus with a degree of sensitivity not heretofore attained.

To this end, transurethral electrodes were so designed (fig. 1) that they might be brought in contact with the lateral walls of the bladder and changes in electropotentials recorded on a Grass electro-encephalograph suitably filtered. In a series of studies on human subjects[4, 5, 6] it was found that electromyograms so obtained possessed definite and typical characteristics and further that striking and recurring abnormalities in the records were observed in known pathological states.[7] It was, moreover, determined that intravesical pressure changes paralleled the bio-electric shifts. Therefore, electromyography appeared to represent a highly sensitive method for ascertaining the physiological condition of the bladder in diseased states.

Although strong evidence indicated that the records obtained represented true bio-electric potentials arising within the vesical musculature, this evidence was of an indirect nature,[5] and it was therefore deemed desirable to perform experiments of a conclusive character in order to determine whether the electromyograms as obtained *in situ* from the human subject did, in fact, represent potential shifts without artefacts arising solely from the bladder musculature and not from other tissues. It was also thought that laboratory studies might clarify, to a large extent, our fundamental knowledge concerning the origin of the characteristic bio-electric potentials observed.

To this end isolated bladders from a variety of mammalian forms (dogs, cats, rabbits, guinea pigs and rats) were utilized.[8] The animals being sacrificed by means of a blow on the head to eliminate the known effects of anesthesia. These bladders were quickly dissected, including short portions of the ureters and urethra, and were suspended (with fine silver electrodes attached) in a bath of oxygenated Sollmann's solution at 38 degrees centigrade. The electromyograms obtained from such preparations were found, in all respects, to be indistinguishable in contour from those recorded *in situ* from the human subject (fig. 2, *A* and *B*).

[1] Boyd, M. and Smith, W.: J. Urol., **40:** 513, 1938.
[2] Boyd, M. and Smith, W.: J. Urol., **42:** 410, 1939.
[3] Weyrauch, H. M., Lucia, E. L. and Howard, J.: J. Urol., **51:** 191, 1944.
[4] Corey, E. L., Boyce, W. H. and Vest, S. A.: Fed. Proc., **10:** 29, 1951.
[5] Corey, E. L., Boyce, W. H., Vest, S. A. and French, C. R.: J. Applied Physiol., **3:** 631, 1951.
[6] Corey, E. L., Boyce, W. H. and French, C. R.: J. Applied Physiol., **5:** 38, 1952.
[7] Boyce, W. H.: J. Urol., **67:** 652, 1952.
[8] Corey, E. L.: Fed. Proc., **12:** 29, 1953.

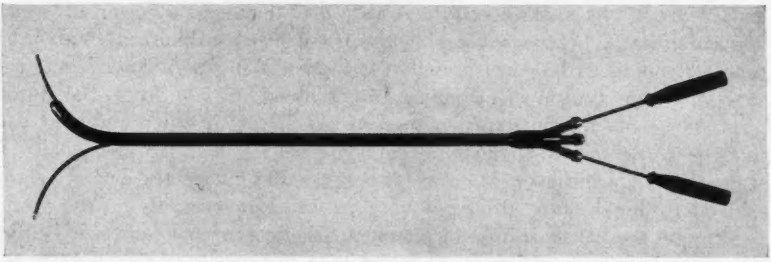


FIG. 1. Transurethral electrode carrier for obtaining electromyograms from the human bladder. Body of instrument contains open passage for filling or emptying bladder, as well as for securing pressure recordings while electromyograms are being made. The two electrodes may be extended or withdrawn at will, and while in use are connected with Grass electro-encephalograph, suitably filtered. (Instrument constructed by American Cystoscope Makers, Inc., New York City, through kindness of Mr. Frederick J. Wallace.)

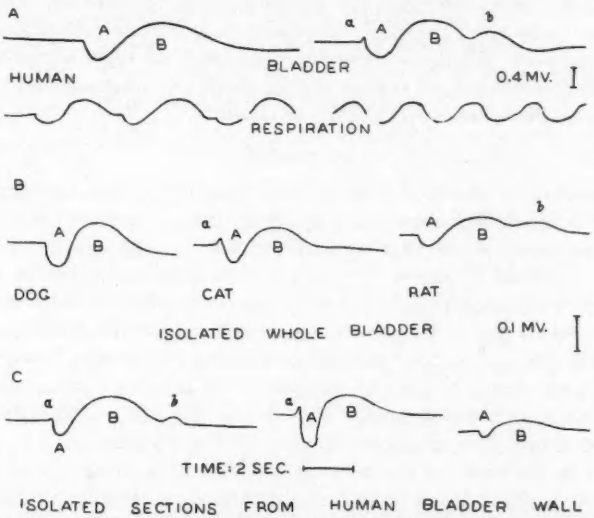


FIG. 2. *A*, two typical tracings from normal human bladder, characteristic wave components "a", "A", "B" and "b". Synchronous respiratory record, obtained by means of nasal thermocouple, is necessary for detection of artefact induced by excessive respiratory movement. (Note lack of relationship to respiratory muscle activity.)

B, electromyograms obtained from isolated bladders of dog, cat and rat. Similarity of these records to those obtained in situ from human subject is apparent.

C, records secured from sections of human bladder obtained at operation. First tracing is from a portion of lateral vesical wall, while second record represents potential changes at entrance of ureter. Right hand figure shows reduced EMF generated in portion of vesical neck.

When such preparations were treated with sympathomimetic and parasympathomimetic drugs as well as with autonomic blocking agents, it was found that the cholinergic drugs in all instances increased the frequency and magnitude of the bio-electric response, while the reverse was true for adrenergic agents. More-

over, adrenergic blockade (dibenzyline) had, in all instances, a powerfully stimulating action while cholinergic blocking agents (such as banthine) either abolished or markedly reduced bio-electric activity. From these experiments it was considered that the typical electromyogram obtained *in situ* from the human subject represents a true record of vesical bio-electric activity and that such activity is in response to cholinergic (parasympathetic) bombardment.

If the above conclusions were correct it appears that bio-electric activity within the bladder should quite probably vary in different portions of the viscus, depending on the concentration of parasympathetic neurones, or nerve endings within the musculature. In order to investigate this aspect of the problem sections of human bladders were obtained at operations necessitating cystostomy, and electromyograms were secured from these tissue slices.

Marked differences in potential were observed. Thus, frequency of potential shift as well as EMF generated were found to be greatest in sections at the entrance of the ureter and from the more central portions of the bladder, while low frequency and potential were observed in tissues from the bladder dome and at the vesical neck (fig. 2, *C*). These findings are in theoretical agreement with the quantitative anatomical studies of Campbell[9] and Swenson[10] on parasympathetic neurone distribution in the human bladder.

DISCUSSION

Electromyograms obtained from isolated bladders in five mammalian forms were found to be indistinguishable graphically from those recorded *in situ* from normal human subjects, so that we consider that the electromyographic pattern previously described by us[4, 5, 6, 8] is quite definitely the result of bio-electric changes within the bladder musculature. Slater[11] has also recently confirmed our findings as regards the contour of the electrocystomyogram utilizing needle electrodes thrust into the bladder musculature during cystoscopy. However, no observations made either on human subjects or on intact animals can offer such conclusive evidence concerning the origin of the electropotential shifts described as can these reported experiments utilizing the excised organ.

In regard to the origin of the bio-electric changes recorded, one is admittedly on less certain ground. It is true that the pharmacologic studies strongly indicate that the impulse is cholinergic in character. However, until more is known concerning the distribution of parasympathetic post-ganglionic neurones, as well as cholinergic fibers within the bladder musculature, some uncertainty must attach to our knowledge of the origin of the bio-electric phenomena described. It is, however, considered that the aforementioned experiments furnish strong evidence for the concept that the electrocystomyogram represents the response of the vesical musculature to intense and periodic parasympathetic bombardment, and that in diseased states, alterations in the characteristic pattern of such electromyograms are representative of either a) faulty parasympathetic innervation,

[9] Campbell, M.: J. Urol., **68:** 584, 1952.
[10] Swenson, O., MacMahon, H. E., Jaques, W. E. and Campbell, J. S.: New Eng. Med. Center Bull., **13:** 157, 1951.
[11] Slater, G. S.: J. Urol., **69:** 626, 1953.

or b) an atypical response of the diseased musculature to parasympathetic bombardment.

SUMMARY

Electromyograms obtained from the isolated urinary bladders of various mammalian types are indistinguishable in form from records secured *in situ* from normal human subjects.

The frequency of activity as well as the magnitude of bio-electric potentials observed in excised bladder preparations were increased by the administration of parasympathomimetic drugs and by adrenergic blockade. The reverse was found to be true for sympathomimetic substances and parasympathetic blockade.

Records secured from strips of human bladder musculature (fig. 2, *C*) were identical in contour to those obtained from isolated whole bladders, or from the human bladder *in situ*. Maximum activity was shown by tissue samples from the more central portions of the bladder and electropotential activity was minimal in tissue strips from the dome and from the vesical neck.

These findings indicate that the electrocystomyogram secured by way of transurethral electrodes placed within the human bladder represents vesical activity in response to parasympathetic bombardment.

ANTIBIOTIC THERAPY OF URINARY TUBERCULOSIS: AN INTERVAL REPORT OF SIX YEARS EXPERIENCE

REED M. NESBIT AND CHARLES C. MACKINNEY

From the Section of Urology, Department of Surgery, University of Michigan, Ann Arbor, Mich.

Over six years have now elapsed since the advent of antibiotic therapy in genito-urinary tuberculosis. In a preliminary report[1] 2 years ago, the cases of 64 patients treated at the University of Michigan Hospital for tuberculosis of the urogenital tract were reviewed. The present communication is a follow-up study of this original group together with data on 26 additional patients treated since that time. The most recent cases have been observed for a minimum period of 6 months after the completion of antibiotic therapy.

INCIDENCE

Of the 90 patients treated in this series, 57 were males and 33 females. The age of the patients varied from 18 months to 72 years with over two-thirds being between the ages of 20 and 50 years. The presenting signs and symptoms are summarized in table 1.

Fifty-three of the patients had concurrent active tuberculosis apart from the genito-urinary tract or gave a history of it. Forty-four of the 57 male patients had positive clinical evidence of genital involvement.

MODE OF TREATMENT

During the first 2½ years of study the patients received streptomycin in doses of 1.0 to 2.0 gm. daily for periods varying from 40 to 120 days. Since that time dihydrostreptomycin has been given, using a basic regimen of 2.0 gm. daily for 90 days. Seventy-five per cent of the patients in this latter group received a total of 180 gm. dihydrostreptomycin in 90 days. Because of circumstances arising during therapy, the remainder received variations from this basic program. Antibiotics have been used to augment rather than supplant the well established principles used in combating tuberculosis, and for this reason sanatorium care during antibiotic therapy and for 6 to 12 months following medication has been considered essential. All cases in this series were studied by cystoscopy, retrograde pyelography and renal function tests; and 24 hour bladder urine as well as individual kidney specimens were tested by culture methods and guinea pig inoculation.

Para-amino salicylic acid has been used in treating our patients since the value of this substance has been recognized, but we have continued to employ daily 2.0 gm. doses of the antibiotic even though most investigators today advocate a smaller dosage given less often. There are certainly valid reasons for the latter regimens but their ultimate value has yet to be assessed. Many phthisiologists have urged us to continue with the regimen of large daily dosage so as to provide a basis for comparison of long term results with other plans of treatment, and

[1] Nesbit, R. M., and Thirlby, R. L.: Results of streptomycin therapy in urinary tuberculosis; A four year review. J. Urol., **68:** 394–398, 1952.

TABLE 1. *Presenting symptom or sign*

	CASES
Irritative bladder symptoms	40 patients
Epididymitis	17 patients
Hematuria	13 patients
Pyuria	13 patients
Flank pain	7 patients

since this series comprises a significant number of cases the policy would appear to be justified until some regimen had demonstrated a clearly defined superiority.

The present program then consists of complete rest in a sanatorium, dihydrostreptomycin 2 gm. daily, and PAS 12 to 15 gm. daily. Isoniazid is used as an addition to this regimen when a second course of therapy is used either for relapse cases or those which fail to respond to the initial 90 day course.

In unilateral renal disease, when small lesions are demonstrated in the pyelogram, antibiotic therapy is administered for 60 days then a check-up examination is made. If substantial improvement has not occurred, nephrectomy is performed and the antibiotic program is continued for another 30 days. If initial pyelograms demonstrate a moderate or advanced destructive process, then nephrectomy is performed after 10 days of antibiotic therapy and the regimen is continued through 90 days. All patients have check-up studies with x-rays at the completion of the antibiotic regimen and at 3 month intervals for the first year; every 6 months thereafter. Urine cultures and animal inoculation studies are carried out monthly for the first year.

RESULTS OF TREATMENT

Unilateral renal disease was treated in 42 patients (table 2). Sixty-seven per cent of this group had normal urine when last examined. Twenty-one of the unilateral cases were treated with nephrectomy as well as antibiotics and 86 per cent of these have remained well. An equal number of unilateral cases did not have surgery and lasting remission occurred in only 48 per cent. The results of medical treatment alone certainly do not compare favorably with the combined surgical and antibiotic regimen in this small group of cases; and the high failure

TABLE 2. *Unilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
No surgery			
Normal pyelograms	13	7	53.8
Minimal abnormality	4	2	50
Moderate abnormality	4	1	25
Total no surgery	21	10	47.6
Nephrectomy—all had abnormal pyelograms	21	18	85.7
Total all cases	42	28	66.7

rate in the cases showing normal pyelograms offer a strange paradox when compared to the high rate of remission that has been observed in the bilateral cases of the present series.

Table 3 summarizes the results of treatment in patients with bilateral renal tuberculosis. There were 30 patients in this group and 76 per cent have enjoyed remissions to date. The majority of these bilateral cases had one kidney removed either prior to the present program of antibiotic therapy or else in conjunction with the regimen. Table 4 enumerates the status of the kidneys in the bilateral cases in which surgery was not performed. It is of interest to note that 4 of 6 patients with significant bilateral pyelographic changes developed normal urine and have not relapsed. X-rays in 2 of these cases are of considerable interest so are included in this report (figs. 1 and 2).

Eighteen patients had negative kidneys but had tuberculous cystitis and/or genital involvement. Ten of these had a previous nephrectomy with the remain-

TABLE 3. *Bilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	8	7	87.5
Previous nephrectomy, abnormal x-ray	5	4	80
Nephrectomy with treatment normal x-ray remaining kidney	4	3	75
Nephrectomy with treatment, abnormal x-ray remaining kidney	1	1	100
No surgery	12	8	66.7
Total	30	23	76.6

TABLE 4. *Bilateral renal disease without nephrectomy; results classified according to pyelographic findings*

PYELOGRAMS	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Normal to minimal abnormality on both sides	2	1	50
Normal to minimal abnormality on one side Moderate to advanced abnormality opposite side	4	3	75
Moderate to advanced abnormality on both sides	6	4	66.7
Total	12	8	66.7

TABLE 5. *Residual cystitis and/or genital tuberculosis*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	10	8	80
Normal x-rays, kidney urines negative	8	6	75
Total	18	14	77.7

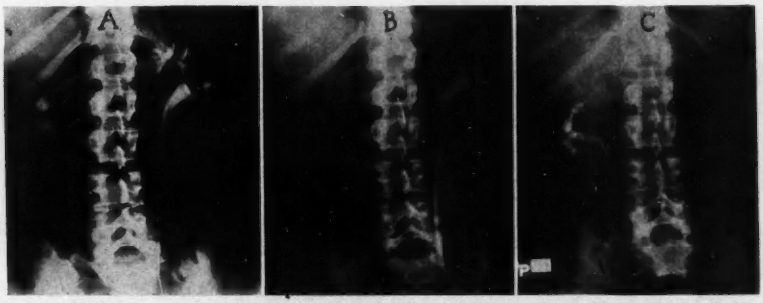


FIG. 1. V. T., a woman aged 29 with bilateral renal tuberculosis. History of pulmonary tuberculosis 1941; Potts's disease 1945. *A*, pyelogram, June 1948, prior to treatment. Patient was given streptomycin 2 gm. daily for 113 days (June–October 1948). Urine became negative after treatment and has remained negative until present time. *B*, 13 months after treatment. *C*, 4½ years after treatment. Note evidence of function on left side revealed by filling of micropelvis with excreted contrast medium. Patient has remained clinically well, and urine has been free from tuberculosis 4½ years.

ing kidney clinically free of disease. The remaining 8 patients had normal pyelograms as well as negative culture and guinea pig studies from both kidneys, yet had tubercle bacilli in the voided urine. Fourteen of these patients had a favorable response to therapy (78 per cent). The results are summarized in table 5.

SUMMARY OF RESULTS

Sixty-five of the 90 patients have had a conversion of urine to negative and have remained clinically free from urogenital tuberculosis 6 months to 6 years after treatment (table 6). Fifty-five had favorable response after one course of therapy, while thirty-five were initial failures or else relapsed after a temporary remission. Twenty-four of these 35 failures were given a second course of treatment and 9 became free from tubercle bacilli after treatment. Two patients received a third course of treatment and one of these exhibited negative urine after treatment (20 months at the present time), while the other relapsed 10 months after the third course of the antibiotic.

Streptomycin was used in 46 of the 116 courses of treatment and yielded a remission rate of 52.2 per cent, while 58.8 per cent of 70 dihydrostreptomycin courses resulted favorably. There is no significant difference in the 2 groups (table 7).

TOXICITY

Toxic manifestations in the 116 courses of therapy are summarized in table 8. In this series the incidence of reactions was materially greater with streptomycin although this antibiotic had the advantage of producing no apparent damage to the auditory branch of the VIII cranial nerve.

ANALYSIS OF FAILURES

In 25 cases the patients failed to respond favorably to therapy. This group represented 51 failures when measured in terms of total courses of treatment with or without nephrectomy. Table 9 shows the distribution of relapses by the month

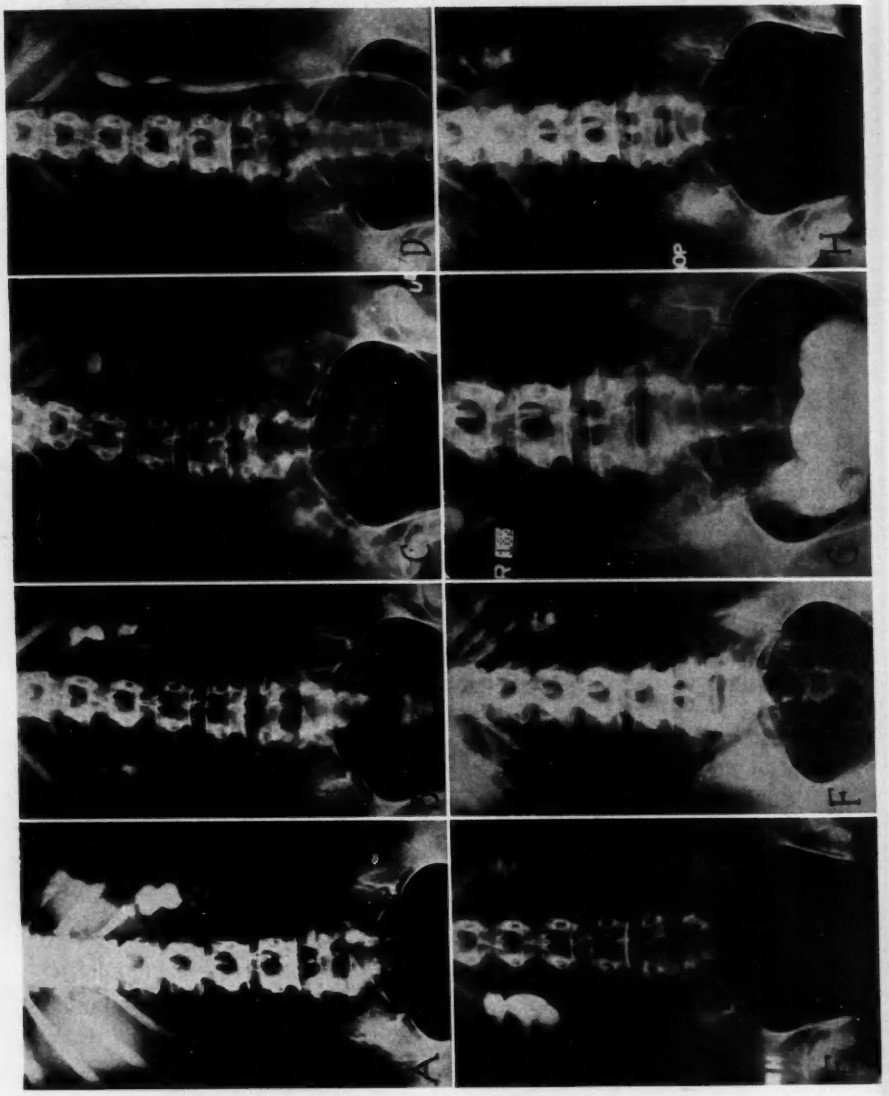


FIG. 2. L. D., a woman aged 22 with bilateral renal tuberculosis proven by culture and guinea pig inoculation of urine from each kidney. History of pulmonary tuberculosis 1943; tuberculous peritonitis 1946. *A*, excretory urogram prior to admission to University Hospital. *B*, retrograde pyelogram (University Hospital) June 1946. Bilateral disease. Note constriction of left renal pelvis. Patient received streptomycin 1.5 gm. daily for 70 days beginning June 1947. Urine normal at end of treatment. *C*, excretory urogram, September 1947, at end of treatment. Note bilateral hydronephrosis. *D*, retrograde pyelogram, September 1947, showing nearly complete stenosis of left pelvis. Right cutaneous ureterostomy, September 1947, because of impassable stricture of right ureteral orifice. *E*, retrograde pyelogram showing improvement of right hydronephrosis 1 month following cutaneous ureterostomy. Note also marked improvement on left that has occurred in 1 month. After 18 months on cutaneous ureterostomy, patient demanded that something be done to rid her of that unhandy device. In April 1949, right ureter was re-implanted into bladder by attaching short upper ureter to tube fashioned from dome of bladder. *F*, excretory urogram made 1 month following re-implantation of ureter. *G*, cystogram made 1 month following re-implantation of ureter. Note reflux. *H*, excretory urogram, October 1952, shows no hydronephrosis in either kidney. On left, upper calyx does not visualize, but constrictive process that was present in pelvis in 1946 and 1947 has cleared completely. Patient now clinically well, and urine has remained free from tuberculosis 6 years. Patient married 2 years ago.

TABLE 6. *Response of urinary tuberculosis to streptomycin and/or dihydrostreptomycin with or without nephrectomy (90 cases)*

	TOTAL	CONVERSION OF URINE TO NEGATIVE
First course	90	55
Second course	24	9
Third course	2	1
Total		65 = 72%

TABLE 7. *Results obtained in 116 courses of streptomycin or dihydrostreptomycin therapy*

	COURSES OF THERAPY	CONVERSION URINE TO NEGATIVE	FAILURE OR RELAPSE	% CONVERSION URINE TO NEGATIVE
Streptomycin	46	24	22	52.2
Dihydrostreptomycin	70	41	29	58.5
Total of all courses	116	65	51	56

TABLE 8. *Reactions to streptomycin and dihydrostreptomycin in 116 courses of therapy*

	COURSES OF THERAPY	VESTIBULAR	AUDITORY	ALLERGIC	% REACTION
Streptomycin					
Less 100 gm	9	0	0	2*	22.2
100–200 gm	27	13	0	1*	51.8
220–300 gm	10	3	0	0	30
Total	46	16	0	3	41.3
Dihydrostreptomycin					
Less 100 gm	14	4	1	1*	37.5
100–200 gm	53	8	5	1*	26.4
200–300 gm	3	0	0	0	0.00
Total	70	12	6	2	28.6
Total all courses	116	28	6	5	34.5

* Drug discontinued.

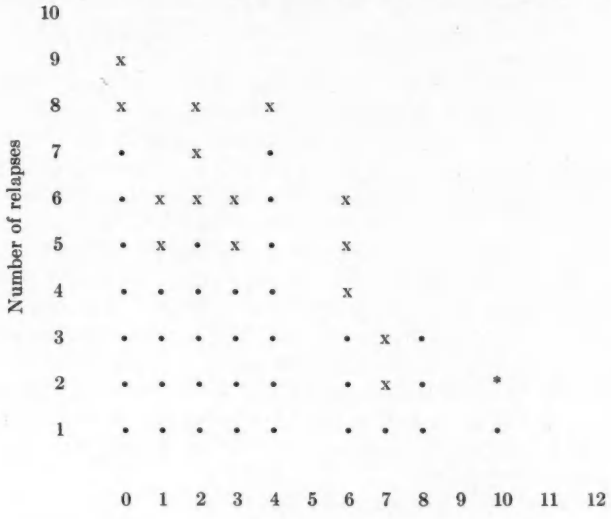
following completion of therapy. It would appear to be significant that the great majority of relapses occurred within the first 6 months, and that no relapses have occurred thus far after 10 months. In this connection it is of interest to note that in the group that Nesbit and Thirlby reported before this society 2 years ago, all of the patients who were then reported to be clinically free from urogenital tuberculosis have remained negative.

For purposes of analysis the 25 patients that failed to respond to treatment or relapsed can be divided into 3 groups:

1) Eleven patients had unilateral renal tuberculosis with normal or abnormal pyelograms on the affected side and were not operated upon. (Three since have had nephrectomy—within the past 6 months).

TABLE 9. *Time distribution of 51 relapses or failures*

• — First course
x — Second course
* — Third course



2) Seven with normal kidneys or who had nephrectomy and antibiotics for treatment of unilateral disease remained positive due to persisting cystitis and/or genital tuberculosis.

3) Seven patients with bilateral disease.

SUMMARY

In a series of 90 patients with urogenital tuberculosis, 72 per cent (65 cases) have exhibited negative urine for 6 months to 6 years following the completion of therapy.

A therapeutic program of 2.0 gm. a day of streptomycin or dihydrostreptomycin for 90 days with sanatorium care 6 to 12 months has been used and still is advocated, along with the uses of PAS and isoniazid. It is our purpose to continue with this plan of therapy in the hope that a comparison with reports of other series of patients who are treated with other programs may eventually reveal just what plan of treatment is the best in yielding long term results.

DISCUSSION

DR. CLYDE L. DEMING (New Haven, Conn.): I would like to ask Dr. Reed Nesbit if he is in full accord with the French decision with regard to tuberculosis of the kidney? When a permanent lesion persists, which can be readily discerned by x-ray, would you remove that kidney?

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): Dr. Nesbit, have you any data on the proportion of extra-urinary tuberculosis as compared with genito-urinary tuberculosis in your area, as compared to other areas?

I have had the impression—whether or not it is with justification—that maybe the milk supply regulations of different areas are responsible to some extent for the incidence of genito-urinary tuberculosis. I have the impression that your milk regulations in Michigan—as compared, for instance, to Washington, D. C. —are relatively lax, and I also believe that the incidence of genito-urinary tuberculosis in Washington, D. C., compared with Michigan, is considerably lower.

DR. GILBERT J. THOMAS (Santa Monica, Calif.): I want to emphasize in the discussion of Dr. Nesbit's report that "the patient" is concerned with treating or curing himself. Dr. Nesbit very properly prescribes and continues sanatorium treatment for his patients which means for that patient, an opportunity to develop that something we call resistance so that he, the patient, can control or possibly cure his tuberculosis.

Dr. Nesbit mentioned the many and varied methods of applying anti-tuberculosis agents i.e., chemotherapeutic agents or antibiotics, etc. All seem to have some effect on the activity of the Microbacterium tuberculosis, but the patient still has to cure himself.

When the antibiotics and/or the chemotherapeutic agents rid the urine of bacilli of tuberculosis and then they recur again in the urine, what has happened? I think the patient's specific tissue resistance and possibly some local effect produced by the chemotherapeutic or antibiotic agents cause a tissue change around the local lesion; it is walled temporarily but may again become active and may not heal. In certain instances it has been necessary, as Dr. Lattimer showed, to resect that portion of the kidney which contains this sclerotic but unhealed area. No antibiotics or chemotherapeutic agent via the blood stream can reach this unhealed area in sufficient concentration. Why? This specific process of healing produces this terrific scar which is a vascular area with much endarteritis so that there is practically no blood supply to this area.

Now I wonder if we can reactivate, i.e. overcome the endarteritis and dense scar by graded doses of tuberculin and when activity is again obtained, can and will the antibiotics and chemotherapeutic agents have their usual effect on the bacilli that are now in the blood stream in the urine or sputum? This method of therapy was a dangerous one before the advent of antibiotics and chemotherapeutic agents.

An important observation was voiced by Dr. Herbst. During the 15 years that I was studying tuberculosis, the occurrence rate dropped 100 per cent in our

county which was well controlled. Today in large teaching hospitals—except those that have an adjunct state or county tuberculosis sanatorium—genitourinary tuberculosis is infrequently seen.

This report is an excellent one. It shows what can be done with a combination of the patient's ability to cure his tuberculosis or his specific resistance, the use of the chemotherapeutic and antibiotic agents and surgery.

DR. FLETCHER H. COLBY (Boston, Mass.): It is an unpredictable disease. We have had patients at the Lakeville State Sanatorium in Massachusetts who have apparently been well for 10 years, and then the disease has shown up in the remaining kidney.

We recently had 2 patients who had been perfectly well after unilateral nephrectomy—one for 30 years and one for 33 years—and then the disease appeared in the remaining kidney.

I think it is extremely difficult to say how long these antituberculous drugs should be given. Our impression at Lakeville is that these patients should be kept on streptomycin, 1 gm. twice a week, or PAS, 12 gm. a day, if they can take it, and isoniacin, about a hundred milligrams three times a day. That is for an indefinite period; several of our patients have been on this routine now for about three years.

DR. J. A. C. COLSTON (Baltimore, Md.): May I ask—along what Dr. Thomas said—if you have found any indications for doing a partial resection of the kidney, as had recently been described in the French literature, and also in the Swedish literature?

DR. DAVID M. DAVIS (Philadelphia, Pa.): It seems to me that in certain cases the toxic manifestations—particularly the vestibular and auditory—constitute a most extremely serious complication, and I would appreciate a word from Dr. Nesbit as to what he has done about that.

DR. REED M. NESBIT (Ann Arbor, Mich.): This is a problem that we are going to have with us for a long time.

Several questions have been asked. First of all, Dr. Deming inquired, I believe, whether we believe that a persisting lesion demonstrated by x-ray, in which the urine becomes negative, should be treated surgically.

I would say "No." We have such cases. Some of them are bilateral and some of them are unilateral.

The question of partial resection of the kidney has come up since the recent publications in Europe. We were going to do this in one of our cases where there was a tiny lesion demonstrated by x-ray. This was a unilateral case. At time of operation we found that the patient had a large amount of tuberculosis in the kidney. We didn't even suspect what was present, by pyelography, so I don't know whether the pyelograms tell you too much about it. You are all as familiar with that as I am.

As to the question about the incidence, Dr. Herbst, I can't answer that. In Michigan we believe we have a health department that has been very active and very careful in examining all of the dairy herds. It has done that for a large number of years. Whether this disease is milk-borne, I don't know.

A few years ago, upon visiting Dallas, Texas, I was interested to have Dr. Folsom ask me to see a patient who had a lesion in the epididymis. He left me in a room with this patient and was gone about half an hour, then he came back and asked, "What's the matter with the man?"

I said, "I don't know. What is it? What do you want me to discuss with you?"

"Well," he said, "what's the trouble with him?"

I said, "He has tuberculous epididymitis. What's the problem?"

He said, "That's the thing I wanted to ask you about. Does he have it? I've never seen a case before in my life. We don't have tuberculosis in this area of the United States."

The toxic manifestations of antibiotic therapy, of course, are something that the small dosage advocates are trying to avoid. One of my colleagues in the University of Michigan, a professor in the department of surgery, was dying of bilateral renal tuberculosis over six years ago, but now he is working every day as a surgeon. He completely lost his vestibular sense, and sometimes when he walks now, in unguarded moments, you would think he was drunk, because he staggers, but he says that the loss of his vestibular sense is a small price to pay for being alive and well today, six years after treatment.

PATHOGENESIS OF RENAL FAILURE

JOHN T. MacLEAN

We are concerned primarily with the mode of development of the lesion in the kidney which leads to the production of acute renal failure. It is presumed that the pre-renal causes of failure such as a diminished fluid intake, a reduction in the constituents of the blood as occurs in haemorrhage, diarrhoea and vomiting have been excluded. Likewise it is presumed that the post-renal factors which cause obstruction to the outflow of urine have also been excluded.

This process of elimination narrows our problem down to the specific problem of what is occurring in the intrinsic renal lesion, and what are the contributing factors in its production. Figure 1 represents a diagrammatic concept of the various contributing factors which will be discussed in more detail subsequently.

A. GLOMERULONEPHRITIS

Figure 2 shows a normal glomerulus. It is not difficult to visualize that in an acute inflammatory reaction the polymorphs rush to the scene of action, so that very soon the entire glomerulus becomes a seething congested mass of inflammatory cells (fig. 3). In addition, Bowman's capsule becomes filled with an inflammatory exudate. Likewise, it is not difficult to conceive that if a sufficient number of units are so involved and their function eliminated, that acute renal failure may ensue. Clinically, we are well able to recognize this type of lesion with the sudden onset of mahogany coloured urine, hypertension, marked albuminuria, many red blood cells and white blood cells in the urine, and granular casts, followed in a few days, in some cases, by anuria.

Sulfonamide anuria. Sulfonamide anuria should be mentioned and excluded. Its mode of onset may vary considerably. There are four types of lesion possible: 1) Seventy-five per cent are due to mechanical blockage of the ureters by mixed blood clot and crystals. We have had 3 cases of sulfonamide anuria admitted within the past month. All three were due to sulfamerazine. All three had mechanical obstruction of the ureters with blood clot and crystals. All three promptly recovered when the ureters were catheterized and the pelves washed out. The lesion may be 2) toxic glomerulonephritis, 3) focal necrosis, or 4) a lower nephron-nephrosis type of lesion with disruption of the tubule at several points along its course.

Bilateral diffuse cortical necrosis should also be excluded. This lesion is defined by Duff and Moore as a pathological entity of unknown cause manifested by extensive uniform necrosis of the cortex of both kidneys. There are two theories of origin: 1) that it is due to toxins, as in pregnancy; 2) that it is due to ischaemia causing vascular occlusions. Clinically there is oliguria, anuria, and pain, usually epigastric, radiating along the ureters. Edema of the dependent parts occurs. The outcome is usually fatal; however, a very few patients do recover.

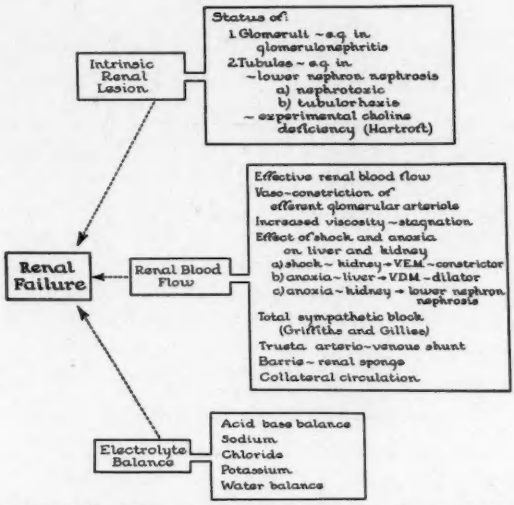


FIG. 1. Diagram indicating main contributing factors in production of anuria

FIG. 2. Normal renal glomerulus showing afferent arteriole

B. TUBULES

A considerable amount of interest has centered around the lesion in the tubules. The exact sequence of events leading up to the production of "lower nephron nephrosis" still remains a matter of conjecture.

Lucké in 1946 gave an excellent description of the microscopic lesion, as being one of edema of the cells lining the distal convoluted tubules, followed by degeneration and necrosis of these cells. Numerous haem casts are also present. These are made up of myohaemoglobin and haemoglobin. There are two views held regarding the appearance of haem casts in the tubules. One is that haemo-

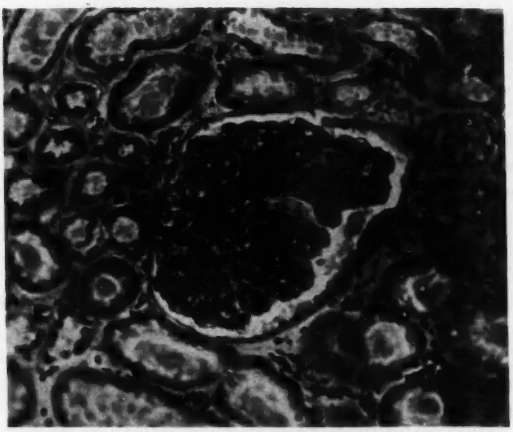


FIG. 3. Renal glomerulus in acute glomerulonephritis. Note inflammatory cells in glomerular tuft and protein exudate in Bowman's capsule.

globin may dissociate into molecules of smaller size and pass through the glomerulus, whereas myohaemoglobin is allowed to pass because of the increased permeability of the glomerulus. The other view is that these two compounds settle out in situ, from the debris locally present.

Much of the current work on this problem is divided into two phases: a) original investigation; b) a determined effort to eradicate the name and substitute another which renders the concept of pathogenesis even more opaque.

There are many names in medicine that are in their true sense misnomers, and yet have survived the years. The main objection to the name "lower nephron nephrosis" is that the lesion is not limited to the lower nephron, and that it is not a nephrosis but a nephritis. These seem like legitimate objections. However, if one concedes all this, it would still appear to be a reasonably good name.

Oliver et al. in 1951 reported on his investigations following the study of cases in which the individual nephrons were dissected out and studied. He believes that there are two types of lesion which may occur: A) Nephrotoxic damage. This occurs for example in mercury poisoning. The lesion is present only in the proximal convolutions, and is evenly distributed amongst all the nephrons. Debris may be packed within the lumen of the tubule, but the basement membrane remains intact. At the commencement there is a hydrops of the tubular cells followed by flattening of the epithelial cells, and death of the cells.

b) Tubulorhexis. Here there is disintegration of the tubular membrane; the epithelial cells become necrotic. This may involve only a portion of the wall of a tubule, or the whole wall may be involved resulting in loss of continuity. The lumen of the tubule thus lies open to the surrounding interstitial tissue. The interstitial reaction may be nil or it may be extreme. There may be masses of connective tissue fibres surrounding the tubule, or the surrounding reaction may be granulation tissue. This type of lesion is found in every segment of the nephron,

but is most common in the terminal portion of the proximal convolution where it dips into the medulla, and in the distal convolution and connecting tubule.

What occurs next? In the portion of the tubule involved with the nephrotoxic edema and death of the cells, regeneration of the cells occurs, but function is not necessarily restored. In the tubulorhexis type of lesion, if there is some continuity of the tubule, regeneration may occur; whereas if the tubule is completely divided, it may never unite, or the ends may be invaded and obstructed by growing granulation tissue extending from the interstitial tissue.

One may reasonably question the isolationism of this theory of nephrotoxic damage. It is assumed that most toxins are more concentrated in the proximal tubule than elsewhere, and that the lesions they produce should be most intense in this region, and be continuous rather than segmental. Microscopically this is what actually does occur. On the other hand, it is rather difficult to imagine that a toxic substance in solution should suddenly loose its toxicity once it has passed a given point of the tubule. Oliver et al. state that more distal portions of the tubule do show tubulorhexis or disintegration of the tubular membrane, although in the crush syndrome the nephrotoxic lesion in the upper nephron is completely lacking.

In tubulorhexis when there is disintegration of the continuity of the tubular membrane, it is not surprising that there should be an interstitial tissue reaction. This is exactly what one would expect, and is precisely the same as what happens when the interstitial tissue is invaded by any other process such as occurs in pyelonephritis. In the latter, the response is inflammatory in nature.

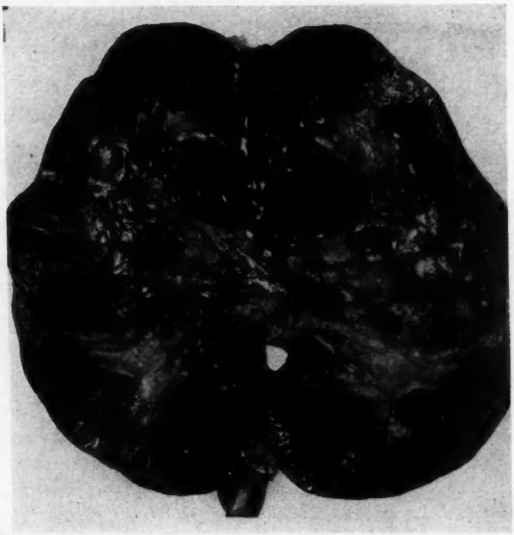


FIG. 4. Case No. 48-13883. Gross appearance of kidney in patient who died after partial recovery from acute renal failure. Anuria developed following a 12 hour period of hypotension postoperatively. Urinary output returned on the sixth postoperative day. Death occurred following evisceration of wound on sixteenth postoperative day.

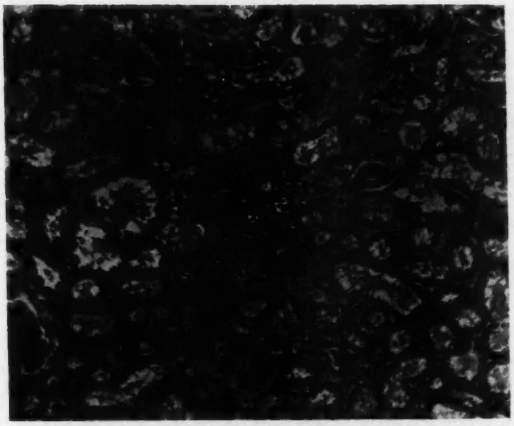


FIG. 5. Same case as figure 4. Microscopic section showing marked interstitial edema. Is it this edema which is choking off blood supply?

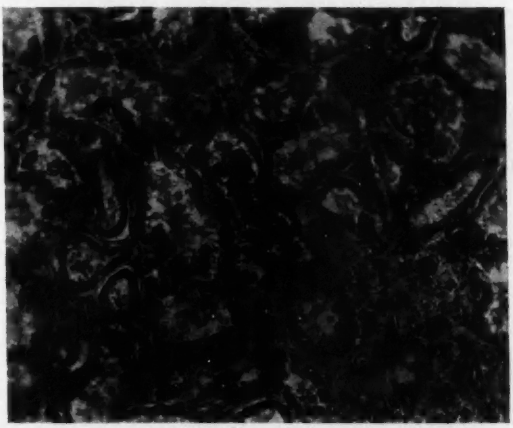


FIG. 6. Same case as figures 4 and 5. Microscopic section of another area showing haem pigment cast in tubule.

Figures 4, 5, 6, 7, and 8, from the author's cases, show some of the lesions described.

RENAL LESIONS IN EXPERIMENTAL CHOLINE DEFICIENCY

Hartroft has produced the "haemorrhagic renal syndrome" in experimental choline deficiency in weanlings and adult rats, and has described the pathogenesis. The initial lesion consists of the intracellular formation of sudanophilic droplets in the proximal convoluted tubules. He believes that the rapid appearance of the droplets may be responsible for the associated tubular swelling. This in turn causes pressure on the capillaries supplying the tubules, with resultant ischaemia and eventual necrosis of the tubules.

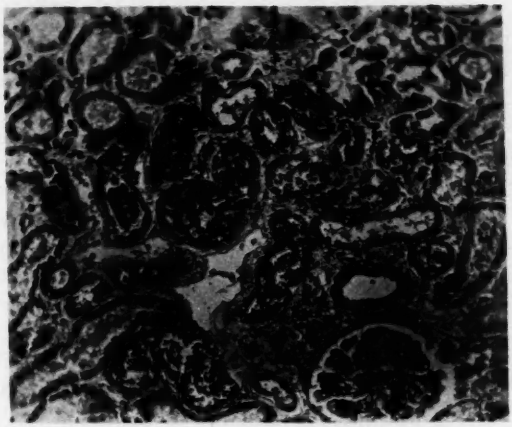


FIG. 7. A-14194, case of retroplacental haemorrhage with death in uremia. Section shows casts in tubules with marked edema and infiltration around tubule. Tubule in lower left hand corner is disrupted (tubulorhexis).

FIG. 8. A-14284, case of post-transfusion anuria. Section shows haem cast in tubule. Note that it is focal lesion, and that tubule both before it and after it is normal.

There would appear to be an extraordinary similarity between this type of lesion, and the nephrotoxic lesion described by Oliver et al.

In seeking a common denominator to explain the changes found in lower nephron nephrosis we must consider still other possibilities which might contribute to the production of this lesion. Referring back to figure 1, these are: the effects of:

1) Effective renal blood flow
2) Vasoconstriction of the efferent glomerular arterioles
3) Increased viscosity of the blood plasma, and stagnation

4) The effect of shock and anoxia on the liver and kidney
   a) Shock—Kidney produces V.E.M.—Vasoconstrictor
   b) Anoxia—Liver produces V.D.M.—Vasodilator
   c) Anoxia of kidney produces lower nephron nephrosis
5) Total sympathetic block
6) Trueta arteriovenous shunt
7) Barrie—Renal sponge
8) Collateral circulation

1) *Effective renal blood flow.* In man, 95 to 97 per cent of hippuran or diodrast added to human blood can be recovered from the plasma within 3 minutes. If for example 700 mg. of diodrast is excreted by the kidney in 1 minute, and the blood plasma has a content of 1 mg., it follows that 700 cc of plasma must have passed through the kidney in that period. This in turn represents a blood flow of 1300 cc per minute which is the normal effective renal blood flow in man for both kidneys.

It is possible to cannulate the renal vein and thereby measure the absolute renal blood flow. In some instances although the actual or absolute renal blood flow may remain unchanged, the effective renal blood flow may be considerably reduced as determined by para amino hippuric clearance tests.

Maluf, using India ink injections, has demonstrated in dogs that during the anuria or oliguria which follows the infusion of lysed red cells superimposed on reversible shock or dehydration, the cortex and medulla are equally injected with the dye, indicating a normal absolute blood flow, but there is a marked fall in the effective renal blood flow (as measured by renal clearance of para-amino hippurate), due to the inability of the obstructed tubule to allow the passage of hippurate.

This was also well shown in one of the cases described in detail by Oliver et al. The patient was admitted to the hospital following the ingestion of anti-freeze mixture. The amount taken was unknown. He was admitted complaining of bilateral renal pain and dyspnea. Red blood cells and albumin were found in the urine. On the twelfth day the urine excretion was 0.2 cc per minute. The blood urea nitrogen was 266 mg. per cent and the para-amino hippurate and inulin extractions were zero.

The effective renal blood flow is lowered a) when the blood pressure is lowered, as in shock; b) when the blood volume is lowered as in haemorrhage, or marked dehydration; c) in crush and the lower nephron nephrosis type of lesion.

2) *Vasoconstriction of the efferent glomerular arteriole.* Some workers believe that the lesion in lower nephron nephrosis is initiated by a vasoconstricton of the efferent arteriole leaving the glomerulus. This in turn causes a stagnation of blood leaving the glomerulus, and is progressive in a retrograde manner to the glomerular tuft. Since the blood supply to the tubular portions of the individual nephrons is derived almost exclusively from the vascular network formed from the efferent glomerular arteriole, it follows that if vasoconstriction occurs, there results an ischaemia, which in turn produces anoxia of the tubules, leading to their degeneration.

3) *Increased blood viscosity leading to stagnation.* It is recognized that in uremia there is an increased vicosity of the blood plasma. This in turn may increase any stagnation already present in the renal circulation.

4) *The effect of shock and anoxia on the liver and kidney.* Shock is a clinical syndrome which is the result of a malproportion between the circulating blood volume and the volume of the vascular capacity, leading to metabolic changes which may be reversible or irreversible. If the blood pressure and blood volume fall, anoxia of the tissue occurs.

In reversible shock, the organism attempts to compensate for this constriction of the blood vessels of the skin, spleen, etc. to make blood available for the heart. During the anoxic period, the kidney produces a vasotropic substance V.E.M. which causes constriction of the arterioles. This in turn tends to maintain the blood pressure by diverting the blood from the periphery, and making it available to the essential organs, thus leading to recovery from the shock.

Anoxemia of liver: If, however, the stage of shock is continued beyond a certain period, the process becomes irreversible. The continued anoxemia exerts its effect upon the liver resulting in an altered metabolism, and the production of a vasodilator substance V.D.M. This substance has the opposite effect to V.E.M., and causes dilatation of all the arterioles of the body, resulting in pooling of the blood in the capillaries and arterioles.

Anoxia of kidney: Glomerular filtration depends on the blood flow through the kidney, and blood pressure. In shock there is decrease in the blood flow through the kidney at a diminiished rate, and consequently there is a diminished volume of filtrate produced. This small amount of urine is reabsorbed by the tubules so that oliguria occurs, giving a urine with a high specific gravity. The tubules are as yet unaffected. The nonprotein nitrogen rises, but this is due to failure of filtration i.e., extrarenal uremia.

However, if the anoxia is maintained the tubules themselves become damaged and a true lower nephron nephrosis develops. The normal structure is lost and the normal functions of water absorption and selective reabsorption of waste products are also lost. The urine may now flow directly from the tubule into the blood. Haemoglobin casts will be found in the tubules. As the lower nephron nephrosis develops, it becomes a true renal uremia.

When liver damage due to anoxia occurs with renal failure, the condition is called "the hepato-renal syndrome."

5) *Total sympathetic block.* Griffiths and Gillies of Edinburgh working on "Total Sympathetic Block" have produced impressive observations, some of which are entirely contrary to what we have always believed.

In the cases reported, they intentionally produced a total sympathetic block so the surgeon could perform a thoraco-lumbar splanchnicectomy and sympathectomy. Premedication consisted of omnopon and hyoscine. In the anesthetic room, thiopentone was given intravenously, usually 1 gram. A lumbar puncture is done in the second lumbar space, and 150 to 250 mg. of procaine dissolved in 3 to 4 cc of cerebrospinal fluid injected. The patient is turned on his back and placed in sharp Trendelenberg position. This position is maintained until the

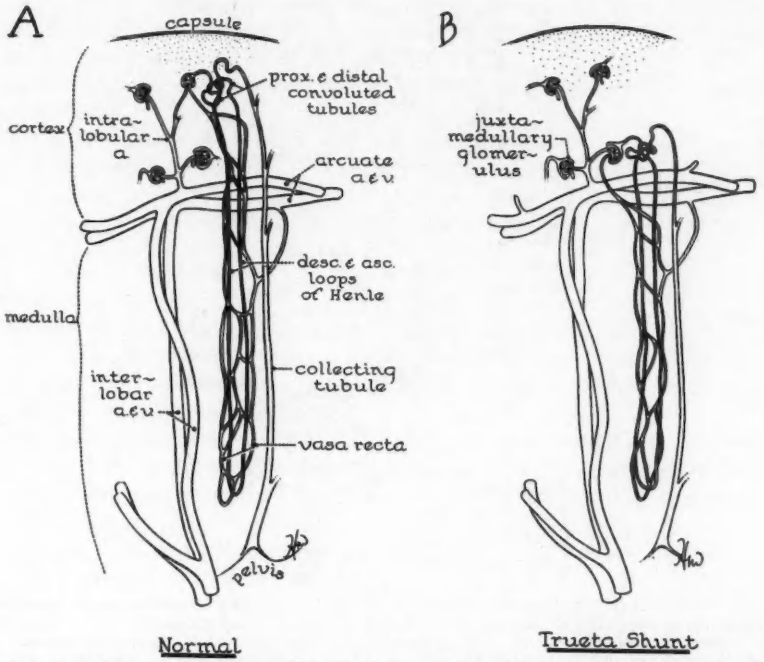


FIG. 9. Indicating normal renal circulation, and diversion through "Trueta-shunt"

blood pressure starts to fall. An airway is inserted, and 100 per cent oxygen administered. The patient is then postured in the lateral "jack-knife" position. The blood pressure drops off to zero and stays unrecordable throughout the operation. The brachial and radial pulses are not palpable. The anesthesia is believed to extend up to and involve the first thoracic area, although this cannot be accurately determined as the patient is given thiopentone intravenously prior to the lumbar puncture.

In most cases an almost ischemic operative field is obtained. They report 84 operations involving 44 patients with only one death. (This patient had a pleural effusion on the opposite side.)

The interesting feature is that they regard the hypotension as perfectly harmless. Clinically, it has always been accepted that a minimal systolic pressure required to maintain effective filtration pressure was 75 mm Hg. They state, "At pressures lower than this, secretion of urine is much diminished and may even cease, but while effective ventilation with oxygen is maintained as in the technique described, viability of the renal epithelium is not endangered; when the systolic pressure rises to the level necessary for filtration, secretion of urine starts". In this series 3 patients showed a reduction in the output of urine during the first 36 hours after operation."

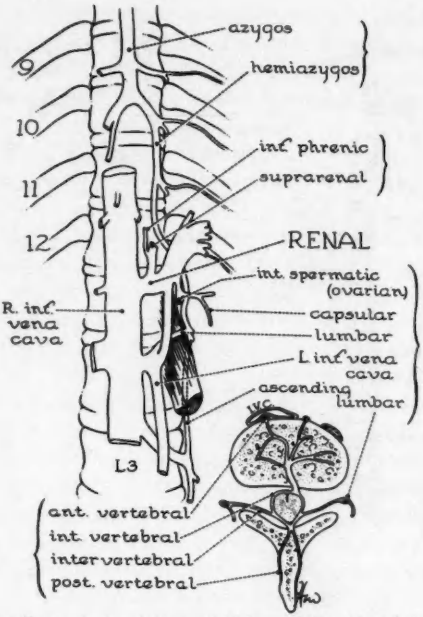


FIG. 10. Showing collateral circulation of kidney. Note that left renal vein is situated at center of a collection of venous channels: 1) inferior phrenic and suprarenal tributaries from above; 2) communications with azygos and hemiazygos vein; 3) communications with set of internal and external vertebral plexuses via intervertebral and lumbar veins. (Modified after Anson: Surg., Gynec. & Obst., **84**: 6, 1947).

The oxygen consumption of the normal and diseased human kidney has been studied by Cargill and Hickman, and by Clark and Barker.

6) *Trueta arteriovenous shunt* (*juxtamedullary glomeruli*). Trueta and his associates have described two types of glomeruli designated cortical and juxtamedullary. The juxtamedullary glomeruli are larger than the cortical. The term cortical glomerulus is used to denote a glomerulus whose efferent vessel is of small caliber and which breaks up to form part of the cortical intertubular capillary network. The term 'juxtamedullary glomerulus' is used to denote a glomerulus whose efferent vessel is of large caliber and which passes into the medulla to divide into vaso recti (fig. 9). These workers believe that the kidney has two potential circulations, a greater and lesser. Under extreme conditions, the blood may pass almost exclusively through one or the other. Experimentally this may be true. Clinically, there is no evidence in man that such a shunt does occur.

7) *Barrie arteriovenous shunt.* Barrie's work on the renal sponge would indicate that the renal medulla may have a blood supply independent of the glomerular circulation. However, the conditions which Barrie described are found only in abnormal kidneys, and are probably not a normal structure. Their relationship to acute renal failure has as yet not been clearly defined.

8) *Collateral circulation.* In certain cases of renal failure due to mechanical ob-

struction of the inferior vena cava, the collateral circulation of the kidney may be of paramount importance. The anatomy of the pararenal system of veins has been well described by Anson et al. (fig. 10).

On the right side the suprarenal vein and gonadal vein each empties separately into the inferior vena cava.

On the left side, the left renal vein is found to be situated at the center of a collection of venous channels: 1) the inferior phrenic and suprarenal tributaries from above; 2) communications with azygos and hemiazoygos vein; 3) communications with the set of internal and external vertebral plexuses via intervertebral and lumbar veins.

SUMMARY

In seeking a common denominator which would apply to the various factors discussed above, as contributing in the production of acute renal failure due to an intrinsic renal lesion, anoxia of the kidney or part of the kidney would appear to offer the most likely explanation.

The work of Selye on the General Adaptation Syndrome, and the possible effect of ACTH on the pathogenesis of acute renal failure have not been discussed. Although the theories behind this have considerable appeal, it is impossible to draw any conclusions at the present time.

Medical Arts Bldg., Montreal 25, P. Q., Canada

REFERENCES

BARRIE, J.: Direct medullary arterioles and arteriovenous anastamoses in the arcuate sponges of the kidney. Lancet, No. 258, p. 23, 1950.

BARRIE, J.: Personal communication.

CARGILL, W. H. AND HICKMAN, J. B.: The oxygen consumption of the normal and diseased human kidney. J. Clin. Invest. **28:** 526, 1949.

CLARK, J. P. AND BARKER, H. G.: Studies of renal oxygen consumption in man: 1) Effect of tubular loading (PAH), water diuresis, and osmotic (mannitol) diuresis. J. Clin. Invest. **30:** 745, 1951.

DUFF, L. AND MOORE, K.: Bilateral cortical necrosis of the kidneys. Am. J. Med. Sc. **201:** 428, 1941.

GRIFFITHS, H. W. C. AND GILLIES, J.: Thoracolumbar splanchnicectomy and sympathectomy; anaesthetic procedure. Anaesthesia, **3:** 134, 1948.

HARTROFT, W. S.: Pathogenesis of renal lesions in weanlings and young adult rats fed choline deficient diets. Brit. J. Exper. Path. **29:** 483, 1948.

HERBUT, P. A.: Urological Pathology. Philadelphia: Lea & Febiger, 1951.

LUCKÉ, BAULDIN: Lower nephron nephrosis. Military Surg., **99:** 384, 1946.

MACLEAN, J. T.: Acute Renal Failure. Springfield, Ill.: Charles Thomas & Co. publishers, 1952.

MALUF, N. S. F.: Factors inducing renal shutdown from lysed erythrocytes. An experimental study. Ann. Surg., **130:** 958, 1949.

OLIVER, J., MACDOWELL, M. AND TRACY, ANN: Pathogenesis of acute renal failure. The ischaemic episode. J. Clin. Invest., **30:** 1307, 1951.

SELYE, H.: Stress. Montreal: Acta Endocrinologica Inc., 1949.

SHORR, E., SWERFACH, B. W., FURCHGOTT, R. F. AND BAEG, S.: Hepato-renal vasotropic factors in experimental shock and renal hypertension. Trans. Assoc. Amer. Physicians, **60:** 28, 1947.

DIALYSIS IN THE TREATMENT OF UREMIA: ARTIFICIAL KIDNEY AND PERITONEAL LAVAGE

W. J. KOLFF AND CHARLES C. HIGGINS

From the Research Division and the Department of Urology, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio

Conservative management can accomplish more today than could be attained a few years ago. The majority of patients with acute urinary suppression now recover, but their management is difficult and the results are not always satisfactory; death still takes its toll.

The artificial kidney should not be considered a competitor with, but rather as a valuable adjunct to medical management. Moreover, operations, wounds, crushing injuries, infections, and intoxications may so accelerate protein breakdown and the onset of uremia, that there is but little time for medical management. The cases we report in this article illustrate the status of dialysis in the treatment of uremia. The principles, techniques, possibilities, indications and dangers of these procedures are also discussed.

STATISTICAL PROOF THAT THE ARTIFICIAL KIDNEY CAN SAVE LIVES IS NOT AVAILABLE

Statistics concerning the clinical results in terms of survival after treatment with the artificial kidney are irrelevant except perhaps the reports from Korea. Dr. L. Hollingsworth Smith reported at a committee meeting of the National Research Council in Washington (March 18, 1953) that the mortality rate of severely wounded anuric soldiers in Korea was reduced from approximately 90 per cent to 60 per cent when the artificial kidney was employed behind the front lines. However, other conditions may have changed simultaneously. The series of patients treated with the artificial kidney by Merrill's group in Boston or by Alwall in Lund or by ourselves are not comparable with other reviews, since artificial kidneys are employed for unusually severe or complicated cases, and it is usually the complications or the underlying disease that determines the ultimate survival.

A statistically valid proof could be established if alternate patients were treated with the artificial kidney. However, those who have witnessed the dramatic clinical improvement after treatment with the artificial kidney cannot resist the temptation to treat the patient before it is too late. Since the patient's well-being is and should be the primary goal of the physician, we do not treat alternate patients in this manner. A careful evaluation of the improvement in individual patients is the only indication of the usefulness of the artificial kidney that we have utilized thus far.

Stock in a study of 52 cases of acute urinary suppression (14 patients of his own, 11 treated by Bull, Joekes and Lowe and 27 treated by Muirhead, Vanatta and Grollman), attributes only one death out of 11 to accumulation of retention products. Thus he concludes that there is no place for the artificial kidney in the treatment of uremia. Analysis of the causes of death of the 11 patients

revealed that nine had complications that are often observed in severe or long-lasting uremia, such as dehiscence of abdominal wound, pulmonary complications and cerebral hemorrhages. It appears that uremia had been extended in severity and in duration beyond what the human body can endure.

While Stock is to be congratulated on the results of the medical management of his patients, we believe the results could have been further improved by the use of the artificial kidney.

LIFE CAN BE PROLONGED BY DIALYSIS

Evidence that life can be prolonged with repeated dialysis, either peritoneal lavage or the artificial kidney, in patients with anuria or severe oliguria is available. This was noted by one of the authors in his first experience with the artificial kidney in Holland (1943), and it has been the common experience of other workers in this field. Often, the patients succumb later from complications we have not as yet learned to overcome. In dogs, life can be prolonged after bilateral nephrectomy, for a period as long as 25 days with the artificial kidney (Kolff and Fisher, 1952). With peritoneal lavage, it has been possible to maintain life in bilaterally nephrectomized dogs for 40 days (Kolff and Fisher), 69 days (Grollman, Turner and McLean) and 110 days (Houck). These results indicate that the functions of the kidney concerning excretion of retention products and regulation of electrolytes are of primary importance and that other metabolic functions, such as "two consecutive beta oxidations of fatty acids" (Snapper) and formation of ammonia, are not essential for maintenance of life. There also is no doubt that the clinical picture of uremia both in nephrectomized dogs and in patients with anuric uremia may be almost completely reversed by the treatment with the dialyzing methods. Therefore, Grollman has logically concluded the clinical picture of uremia is due to accumulation of retention products since it can be cured by their removal with the artificial kidney; qualification must be made here regarding the development of hypertension. Bilaterally nephrectomized animals, if maintained by dialysis, have a tendency to develop hypertension and cardiovascular changes resembling the arteriolar necrosis of malignant hypertension (Grollman, Muirhead and Vanatta; Kolff and Fisher). These changes are particularly prone to develop if the nephrectomized animal is overhydrated and has an excess of sodium (Leonards and Heisler).

GENERAL PRINCIPLES OF THE TREATMENT OF UREMIA

It would be unfortunate if the medical management of uremia were neglected due to overemphasis on the use of the artificial kidney. Therefore, the most important points in the treatment of acute uremia may be summarized as follows:

1) Restriction of fluid and electrolytes during the period of anuria: not more than 750 ml. of fluid per day to compensate the insensible water loss, unless there is weight loss due to excessive transpiration, vomiting or diarrhea. Sodium is not administered unless it is demonstrably lost or in emergencies to counteract potassium intoxication or severe acidosis. The potassium- binding resins (car-

boxylic resin, sodium salt or hydrogen cycle) can remove potassium in case of hyperpotassemia.

2) Maximum suppression of protein catabolism by administration of a forced-high-caloric regimen (Borst principle). This has been recently discussed (Kolff, 1951, 1952).

3) Prevention or treatment of infection with antibiotics.

4) Avoidance of operation, "*over*" transfusion, and other procedures which may increase protein catabolism and the production of retention products.

5) Removal of retention products and correction of body chemistry by dialysis: the *artificial kidney*, *peritoneal lavage* and *intestinal lavage*.

PRINCIPLE OF THE ARTIFICIAL KIDNEY

In utilizing the artificial kidney, the patient is lightly heparinized to prevent the clotting of blood in the apparatus. Blood is then withdrawn either from a vein with a pump or taken from the radial artery and guided through a system of dialyzing membranes with blood on one side of the membrane and the rinsing fluid on the other side. Dialysis then occurs (Abel, Rowntree and Turner). This means molecules of small size pass through the membrane while larger molecules and blood cells cannot pass through. Fortunately, all known so-called retention products, such as urea, uric acid, creatinine, and phenols, have small molecules which pass through the membrane from the blood to the dialyzing fluid. Water, salts and glucose pass through the dialyzing membrane in both directions, as salts and glucose are added to the rinsing fluid. Retention products are removed, since the rinsing fluid is large in volume or is refreshed. For electrolytes, equilibrium is obtained on both sides of the membrane if dialysis is continued for a sufficient period of time. Therefore, the electrolyte composition of the bath is extremely important. It is possible to deplete, to overload, or to correct the patient's condition as far as the electrolytes are concerned.

Rinsing fluid. The composition of normal plasma, uremic plasma (with low sodium) and rinsing fluid is presented in figure 1 and another example for rinsing fluid with its individual ions is illustrated in table 1. Lactic acid is added to bring the pH to 7.4. The correct pH can be maintained by blowing a constant stream of 10 per cent CO_2 in oxygen through the rinsing fluid or under the hood of the artificial kidney. (If the pH becomes too high, calcium is gradually precipitated as calcium carbonate and 1 or 2 gm. of calcium gluconate should be injected intravenously.)

It will be noted that the sodium in the suggested bath fluid is lower than the sodium in the normal blood plasma. The blood sodium of a patient in uremia is often lower than normal, but correction to a normal level may not be desirable. It may increase the tendency to hypertension, pulmonary edema and cardiac failure. The electrolyte pattern should be determined before treatment. For sodium in the rinsing fluid we utilize the average between normal and the patient's blood sodium.

If the serum potassium of the patient is high, potassium should be given at a lower concentration (0 to 2.5 mEq/L or 20 mg. per cent) than specified in the table and in the figure.

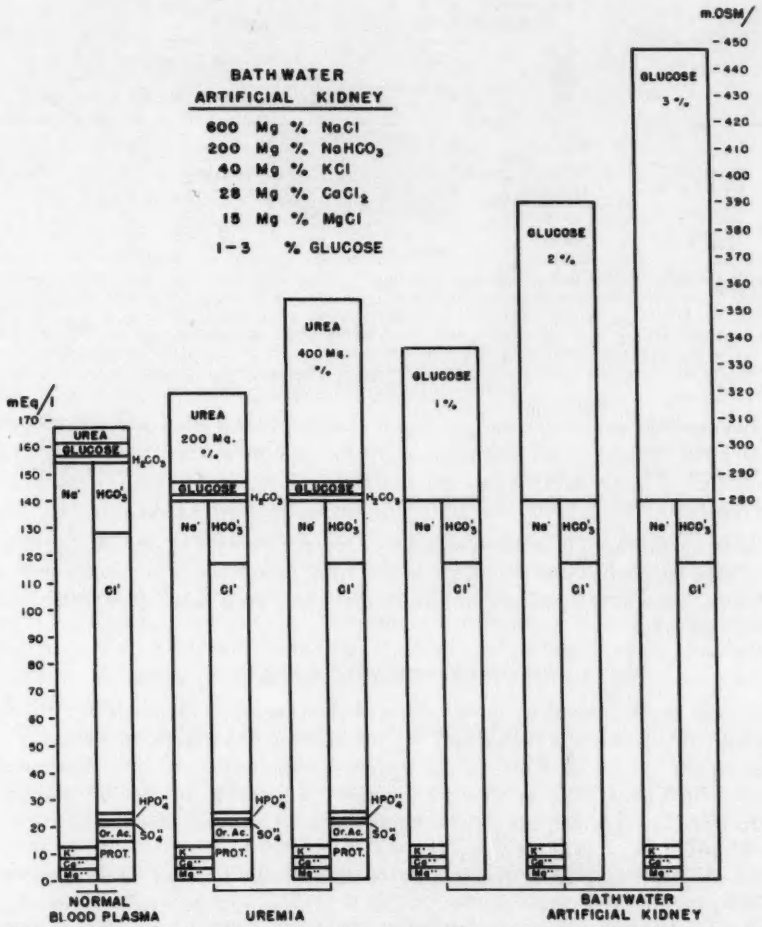


FIG. 1. "Gamble diagram" comparing composition of normal blood plasma, uremic blood plasma, and rinsing fluid for artificial kidney.

For the rotating type of artificial kidney, Wolf (1951, 1952) has calculated that the urea removal may be augmented 16 per cent if the 100 liter bath fluid is refreshed half way through the dialysis; this means after three hours if the dialysis continues six hours, and after two hours if the dialysis terminates in four hours.

As may be seen from figure 7, various amounts of glucose are added to the rinsing fluid. Usually we add 1.5 per cent glucose: 1) to compensate for the osmotic pressure of urea, 2) to compensate for the colloid osmotic pressure of the plasma proteins, 3) to supply calories, 4) to minimize any tendency toward hemolysis, and 5) to extract fluid if edema is present (van den Bossche and Kolff). To remove more fluid, additional glucose is added to the rinsing fluid.

TABLE 1. *Composition of rinsing fluid*

	Mg.%	mEq/LITER					
		Na^+	K^+	Ca^{++}	Mg^{++}	Cl'	HCO_3'
NaCl	600 =	102				102	
$NaHCO_3$	250 =	30					30
KCl	40 =		5			5	
$CaCl_2$	28 =			5		5	
$MgCl_2$	15 =				3	3	
Totals		132	5	5	3	115	30
		145				145	
Total		290 mEq/liter or 286 mOsm/liter					

1% Glucose 1000 ..... 56 mOsm L.
2% Glucose 2000 ..... 112 mOsm L.
3% Glucose 3000 ..... 168 mOsm L.

Lactic acid is added to adjust pH to 7.4.

(Compare with case 1.) Lewis et al. report a weight loss of 4 kg. in 6 hours. However, high concentrations of glucose in the rinsing fluid seem to cause vomiting and drowsiness in the patient. Insulin should be given if high concentrations of glucose are used.

TYPES OF ARTIFICIAL KIDNEYS

Of more importance than the selection of the type of artificial kidney are the men who will operate the device and the organization of a well-trained team. This team should consist of a technician to operate the apparatus, a technician to perform determinations, as the clotting time, a nurse to insure the patient's comfort and a physician for general supervision who should also perform such procedures as the cannulations, etc.

The various types of artificial kidneys have been referred to in previous articles (Kolff, 1950). They can be divided into three groups: Artificial kidneys that work with dialysis only (Kolff, 1947); Guerino and Guerino); artificial kidneys that use dialysis plus filtration (Skeggs, Leonards and Heisler and most other artificial kidneys); and, artificial kidneys that use resins. We will discuss only one type of artificial kidney of each of the two first groups.

Rotating type of artificial kidney using dialysis without filtration (Kolff, 1947). The diagram of figure 2 shows how the blood coming from the radial artery passes through a Fisher and Porter* flow meter, then through a rotation coupling and into the cellophane tubing which is spirally wrapped around the rotating drum. While the drum rotates, the blood seeks the lowest point of the cellophane tubing and consequently runs through the spiral from left to right. There is no

* Fisher and Porter Flow Rater No. B-2-A-127 with ¼ inch diameter glass ball, Hatboro, Pa.

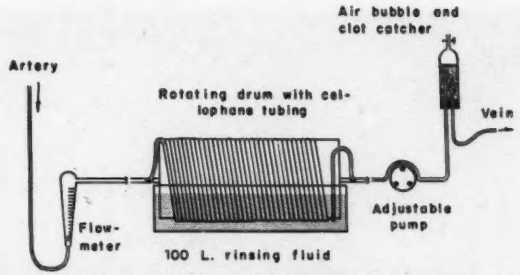


FIG. 2. Diagram of rotating kidney. Blood comes from radial artery; rate of flow is measured by a flowrater and controlled with a screw clamp. Blood passes through hollow axle of drum and enters cellophane tube. Once in cellophane tubing, it moves by gravity when drum rotates. Cellophane tube is not filled like a sausage; just a thin film of blood moves through cellophane. There is no appreciable difference between hydrostatic pressure of blood in cellophane and rinsing fluid outside, hence there is dialysis only, no filtration. A roller pump returns blood to a vein of patient.

difference in the hydrostatic pressure inside and outside the cellophane tubing, and there is no filtration. At the end of the cellophane tubing blood comes into a plastic tube and leaves the artificial kidney through another rotating coupling in the hollow axle of the drum. It is pumped through a clot and bubble catcher and returns to a vein of the patient. There is a continuous flow of blood of approximately 200 cc per minute through the cellophane tubing. The lower half of the drum rotates through a tank with 100 L. of rinsing fluid. However, throughout the rotation the upper part of the drum is continuously dripping wet, so that dialysis takes place over the entire length of the tubing. Two of this type of artificial kidneys are commerically available. One is made by Olsen† the other by Allis-Chalmers.‡ (fig. 3)

The dialyzing tubing (cellophane) is a somewhat refined artificial sausage skin and can be secured from Visking Corporation§ in Chicago.

Stationary types of artificial kidneys. The diagram in figure 4 shows how the blood is pressed either by arterial pressure or by a pump through a system of cellophane sheets or cellophane tubes. The rinsing fluid flows on the outside of the cellophane membranes and the membranes are supported by screens, plastic or rubber ridges. The best and most efficient among these types of dialyzers has been described by Skeggs, Leonards and Heisler, model 2 (fig. 5). The blood touches cellophane on both sides of the blood film, and does not touch the plastic or rubber separating plates. This kidney is not as readily installed as the rotating types, and difficulty is encountered if the cellophane develops a leak. However, it can be used as an ultrafilter when pressure is applied to the blood and suction to the rinsing fluid.

INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

1) *Acute uremia.* There are two schools of thought which are influenced by the facilities that exist for treatment with the artificial kidney. In Boston, where an

† Edward A. Olsen, Ashland, Mass.
‡ Allis-Chalmers, Milwaukee, Wis.
§ Visking Corporation, 6733 W. 65th St., Chicago, Ill.

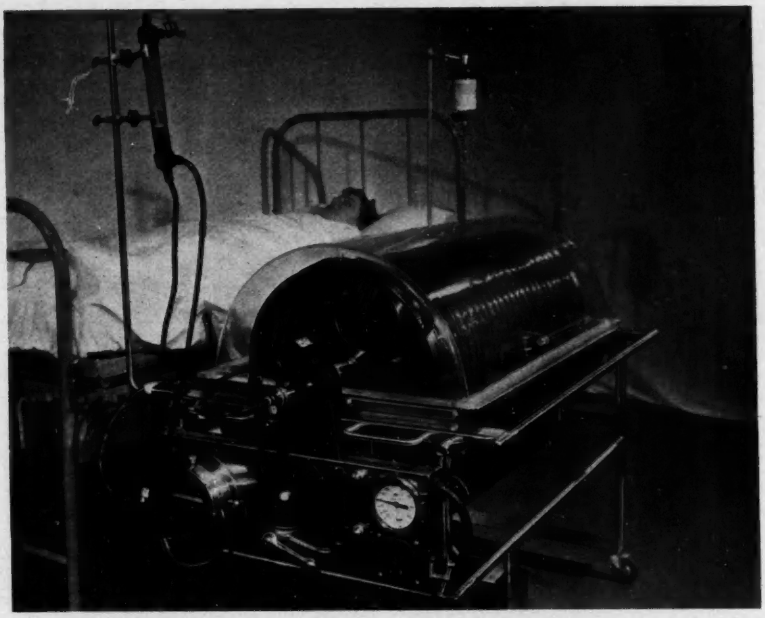


FIG. 3. Rotating type artificial kidney made by Allis-Chalmers. (Reproduced with permission of Mr. H. K. Ihrig, vice-president, Allis-Chalmers.) Cellophane tubing (sausage casing) is wrapped around a stainless steel cylinder. Through lucite hood, one can see last loop of cellophane tubing where it is connected to outflow tube for blood on upper part of cylinder. Outflow tube then proceeds to axle of drum in which a rotation coupling is mounted. Blood is then pumped back via a bubble trap (upper left) into a vein of patient. Roller type pump is on lower left. Inflow for blood coming from radial artery is on other side of artificial kidney. Once in cellophane tubing around rotating drum, blood is propelled by gravity alone. It always tends to seek lowest point of cellophane tubing like in an Archimedes screw. Cylinder rotates with its lower segment through a bath during rotation. Rotation is slow, 25 revolutions per minute. Constant movement of both blood and rinsing fluid is important for a good dialysis. Temperature of bath is thermostatically controlled. All parts in contact with blood can be removed and autoclaved. New cellophane and plastic tubing are used for each dialysis. Cellophane is sterilized by boiling.

FIG. 4. Diagram of filtrating and dialyzing type of artificial kidney. The pump to the left forces the blood through a system of dialyzing membranes. Rinsing fluid (not shown) circulates on the outside of the membranes. As the blood is under pressure, dialysis and filtration takes place.

artificial kidney and team (Murphy, Swan, Walter, Weller and Merrill) is available at any time, there is a tendency to treat the patient with dialysis rather early in the course of acute uremia (Merrill). The reasoning is that the dangers of such treatment are negligible and the clinical course of the disease is much milder if

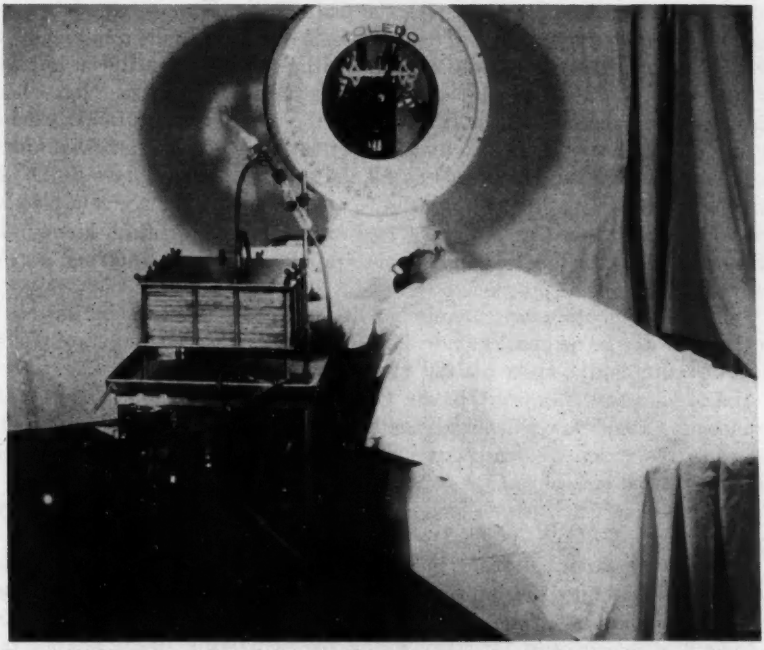


FIG. 5. Stationary artificial kidney by Skeggs, Leonards and Heisler. Tank with rinsing fluid to left. Pump for rinsing fluid and heater is inside the cabinet. Pump for blood projects in front of cabinet. This rubber tube pump sucks blood out of vena cava via a cannula inserted in saphenous vein and presses it through dialyzer seen on top of cabinet. Cellophane sheets are sandwiched in between grooved rubber pads. While blood flows through space between two cellophane sheets, rinsing fluid flows through space between cellophane and rubber pad. Blood returns through an air trap to a vein of patient who is placed on a scale. As this type of kidney is filtrating and dialyzing, a scale is useful to control loss of weight of patient or to weigh combined tanks of in- and outflow fluid which reflects total fluid removed.

uremia is reduced early. This is especially true in older patients, prone to pulmonary and other complications when prolonged bedrest is required. The second school of thought is more or less dictated by the fact that applying of the artificial kidney interrupts the work of busy physicians, requires attention, care, and considerable expense. This leads to an attitude that the artificial kidney should not be employed unless it appears dangerous to wait. The indications for late treatment with the artificial kidney may be considered as: a blood urea level between 300 and 400 mg. per hundred milliliters; a serum potassium level higher than 7 mEq/L and a CO_2 combining power of less than 12 mEq/L. More important than the chemical indications, however, is the clinical condition of the patient. The patient should be treated with the artificial kidney if he becomes progressively restless, irrational or comatose, if the abdomen becomes extremely distended or if it is impossible to maintain a reasonable caloric intake. When there is reason to believe or to hope that adequate diuresis will develop within a

few days, one will tend to postpone the dialysis; however, if for example, the foregoing symptoms are present on the sixth day of mercury poisoning, it is probably advisable not to postpone the treatment with the artificial kidney as in such cases it often takes ten days or more to initiate diuresis. Hemorrhagic diathesis as evidenced by hemorrhages from the mouth or subcutaneous hemorrhages usually responds well to immediate treatment with the artificial kidney. It is possible that the blood used to fill the artificial kidney plays a role. The presence of infection, crushing injuries, large wounds, if not actively bleeding, are additional reasons for beginning treatment with the artificial kidney. The blood urea should be followed and if it rises rapidly, for example 100 mg. per day, dialysis should not be postponed.

The cause of acute anuric uremia has little influence upon the indications for treatment with the artificial kidney. The following is a list of the causes of some cases of acute anuria where dialysis may be considered.

Anuria due to ischemuric episode (Oliver, MacDowell and Tracy), often erroneously called lower-nephron nephrosis. As such are considered, anuria following transfusion accidents, crush syndrome, shock, burns or major operation and hepatorenal syndrome (if it is not a glomerulonephritis plus icterus).

Symmetrical cortical necrosis is probably an extreme form of the same syndrome.

Nephrotoxic poisons. Mercury poisoning and carbon tetrachloride poisoning, etc. Poisons that may cause urinary suppression but less kidney damage, such as salicylate poisoning. The poison itself may be dialyzable.

Acute glomerulonephritis deserves some discussion. Merrill (1952b) has observed exacerbation of hypertension and convulsions in patients with acute nephritis when treated with the artificial kidney. Possibly the endemic acute nephritis observed in Boston may differ from the glomerulonephritis that was observed in more or less epidemic form during and after the war in Holland. Perhaps the use of 140 mEq of sodium in the rinsing fluid for most of the patients in Boston increased the danger of hypertension and convulsions. The danger of such complications made Merrill decide that acute nephritis should not be considered for early treatment with the artificial kidney, unless the patient's life is in jeopardy. Our results in the treatment of severe acute glomerulonephritis have been encouraging. The results for subacute glomerulonephritis plus progressive oliguria are invariably unsatisfactory.

Some examples of acute uremia treated with the artificial kidney are presented.

Case 1 (fig. 6). After drinking an excessive amount of liquor, a 31 year old woman mistook carbon tetrachloride for cough syrup and drank it from the bottle. The following day she unsuccessfully combated her violent distress with additional liquor.

She became anuric, icteric, and vomiting persisted. The liver was enlarged and painful. She was admitted to the Cleveland Clinic Hospital on the fourth day of the anuria. The persistent vomiting rendered oral intake of food impossible.

The weather was unusually warm and the insensible water loss was more than we usually anticipate in patients with anuria. By daily control of her weight, it

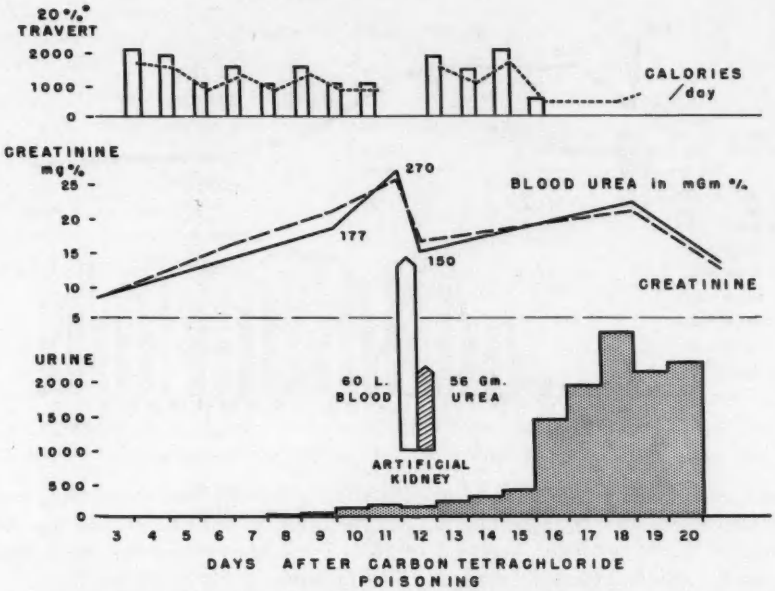


FIG. 6. A 31-year-old patient with CCl_4 poisoning, icterus, enlarged liver, subcutaneous ecchymosis treated with artificial kidney on twelfth day.

was possible to allow 1000 to 2000 ml. of 20 per cent "Travert" (invert sugar Baxter) per day thus providing 800 to 1600 calories daily.

On the eleventh day after the onset of the anuria, she was distended, icteric, irrational, and extremely difficult to manage. The blood pressure was 160/80, and diuresis had slowly progressed from 2 to 180 ml. per 24 hours. Extensive subcutaneous ecchymosis was present. On the twelfth day the blood urea was elevated to 270 mg. per hundred milliliters; the uric acid was exceedingly high in blood plasma; blood creatinine was 26 mg. per hundred milliliters; at this time she was treated with the artificial kidney. Fifty-six grams of urea was removed in 5 hours of dialysis. The blood urea decreased from 270 to 150 mg. per hundred milliliters; creatinine from 26 to 16. Sodium was purposely maintained low, 131 before, 126 mEq/L after dialysis; potassium 5.2 before, 4.6 after; chloride 65 before, 87 mEq/L follwing dialysis; alkali reserve 13.5 mEq/L before, 16 after dialysis. It should be evident that purposely only minor corrections in the electrolyte pattern were made. During the 24 hours of the dialysis, the patient lost 6 pounds of weight, partially because 2 per cent of glucose had been added to the rinsing fluid. The blood flow through the artificial kidney was 200 cc per minute. There was no visible hemolysis. A temporary rise in blood pressure to 220/110 occurred which subsided later. A replacement transfusion of 1100 ml. of citrated fresh blood was administered at the end of dialysis. A total of 205 mg. of heparin had been used. No hemorrhage occurred except oozing from the incisions.

The clinical improvement was dramatic; it appeared better than that which

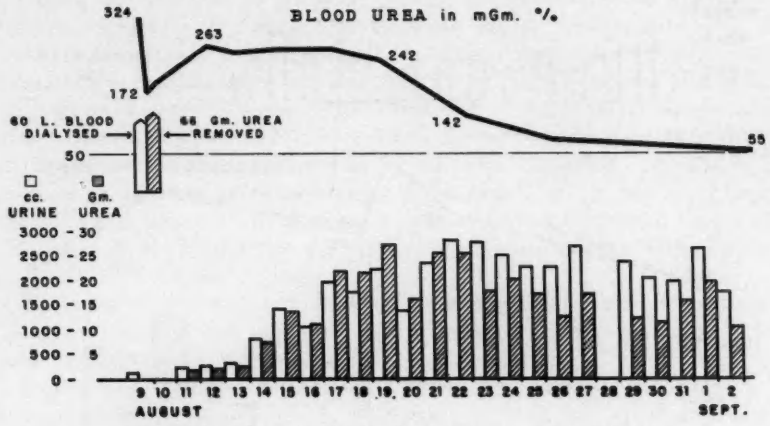


FIG. 7. Man, 54 years of age, with acute glomerulonephritis

might be anticipated from the chemical results alone. She was cooperative and mentally clear. The day following dialysis the urine output was 245 ml.; on the sixteenth day it suddenly increased to 1475. Further recovery was uneventful except for a second temporary rise in blood pressure.

Case 2. Figure 7 is the graph of a man with glomerulonephritis which started 10 days prior to admission. On admission September 8, 1946, he had passed very little urine for the previous 5 days and complained of lack of sleep, headache, nausea and hiccoughing. On examination he showed uremic rash, mild edema; dyspnea; and x-ray of the chest revealed left side cardiac enlargement and pulmonary congestion. The blood pressure was 170/90 mm. Hg. He was treated with the artificial kidney that same day. In 5 hours 66 gm. of urea was removed, and the blood urea dropped from 324 to 172 mg. per hundred milliliters. His blood pressure fell to 125/75 and later to 110/65. It rose slightly during the next few days. At the start of the dialysis, 750 cc of blood which was required to fill the artificial kidney was taken from the patient which improved him subjectively. During treatment an additional 250 cc of blood was removed. This blood was not returned at the end of dialysis. The condition of the patient was most satisfactory after treatment, and diuresis slowly increased. Four weeks after dialysis he was well. He was discharged from the hospital with slight albuminuria and a few red cells in the urine.

Case 3. A 26 year old man swallowed 10 gm. of bichloride of mercury. Two days later BAL was given in large amounts. The blood urea rapidly rose (fig. 8) notwithstanding a forced-high-caloric, low-protein diet. He was completely anuric and had a temperature of 38 degrees Celsius. Penicillin was administered. On the eighth day after taking bichloride of mercury, the blood urea was 337 mg. per hundred milliliters; serum chloride was 90 mEq/L; potassium was 5. It was decided that delay might be more dangerous than dialysis. In 6 hours, 83 gm. of urea was removed. The blood urea fell to 154 mg. per hundred milliliters. After

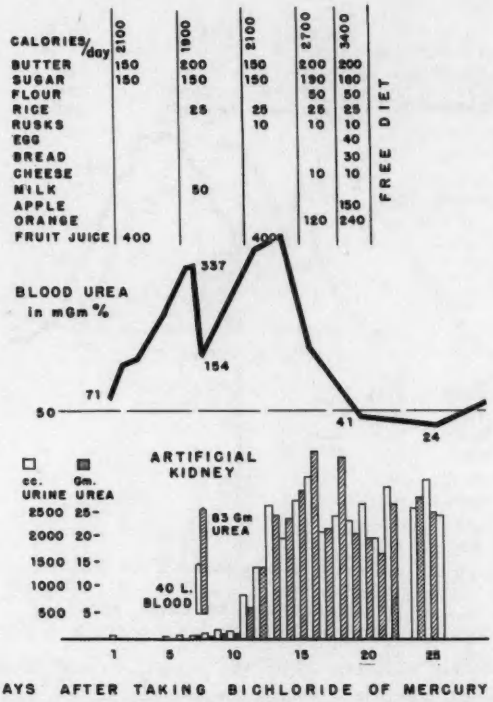


FIG. 8. Twenty-six year old man who swallowed 10 gm. bichloride of mercury

dialysis, his general condition was satisfactory and no undesirable reactions occurred. His blood urea rose again; however, from the twelfth day, his kidney function improved; and by the twenty-first day after taking the bichloride of mercury, the blood urea was normal and the patient was discharged from the hospital.

*Case 4.** A woman, 45 years of age, had a transfusion accident. Acute elevation of temperature, icterus, and anuria developed following blood transfusion after a hysterectomy. Conservative treatment was used with fluid restriction, no salt, and a forced-high-caloric diet without protein. The graph on figure 9 indicates the failure of this therapy.

On the sixth day, she was practically comatose and was treated with the artificial kidney. Fifty-two grams of urea was removed. The blood urea fell from 344 to 288 mg. per cent. The clinical improvement was surprising and better than could be explained by the removal of known retention products. Conservative treatment was continued, but along with a rise in blood urea, the drowsiness increased. A second treatment with the artificial kidney was employed. This time 76 gm. of urea was removed, and the blood urea was reduced from 430 to

* We are indebted to Dr. W. Betist for case reports 4 and 5.

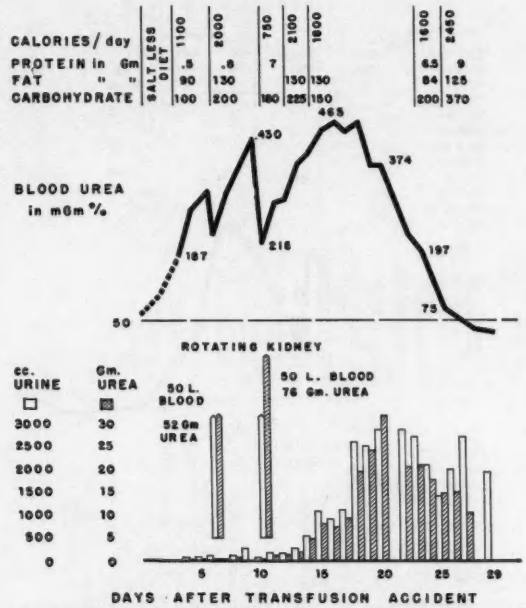


FIG. 9. Ischemuric episode after transfusion accident in 45 year old woman

218 mg. per hundred milliters. Again the patient showed pronounced improvement in her clinical condition. On the fourteenth day, diuresis increased to 500 ml. per 24 hours. It further increased as shown on the graph. The patient recovered completely.

Case 5. This is a report of a patient with hepatorenal syndrome. A woman 38 years of age was admitted to a hospital because of repeated attacks of cholecystitis with icterus, fever and uremia. Her blood urea was 203 mg. per cent. The urine output was less than 300 ml. per 24 hours, and contained .5 per cent of albumin and erythrocytes. The following day cholecystectomy was performed for a perforated, gangrenous gallbladder with peritonitis. The oliguria and rapid rise in blood urea are evident in the graph in figure 10. She was transported to the artificial kidney and before treatment appeared to be extremely ill. There was cardiac failure as evidenced by pulmonary congestion with rales in both lungs. She was icteric and showed acidotic breathing. Though there was evident edema, she was emaciated. The abdomen was distended. The wound edges were edematous and bile discharged from a drainage tube. During dialysis 100 gm. of urea was removed. The blood urea dropped from 597 to 202 mg. per cent. Melena necessitated several blood transfusions. During the following 10 days, it was possible to increase gradually the caloric intake to 2100 calories. Fluid and salt were restricted during the oliguric phase. The urinary output showed a preliminary fall immediately after the dialysis but increased rapidly therafter. A few days after the last date on the graph, the blood urea reached a normal value of 35 mg. per hundred milliliters. She made a complete recovery.

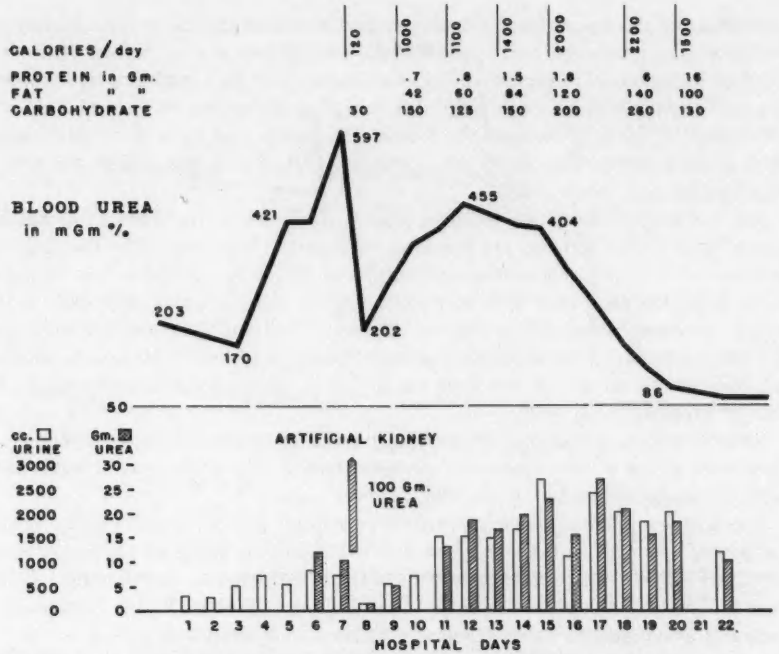


FIG. 10. Icterus cholecystitis and oliguric uremia in 38 year old woman

Acute exacerbation of chronic uremia. Whether this is caused by an exacerbation of a chronic nephritis or by an intercurrent infection, operation or intoxication, it should be treated exactly like acute uremia. It is hoped that equilibrium will be restored and that a useful life may be possible notwithstanding some degree of chronic uremia.

2) *Chromic uremia.* At the subcommittee meeting of the National Research Council in Washington on March 18, 1953, Goldner, Gordon and Danzig reported some of their results of dialysis of patients with chronic renal disease. Of 20 cases of chronic uremia that had been treated carefully before and had shown unsatisfactory improvement, 13 showed a short remission of their symptoms which lasted an average of three days. Seven of the 20 patients, however, showed remissions with an average duration of 2 months. The conclusion at the Peter Bent Brigham Hospital in Boston as quoted by Dr. L. Hollingsworth Smith was that a patient with chronic uremia deserves at least one treatment with the artificial kidney, and that some of the remissions seen after dialysis last for many months. This is in accordance with the experiences of Alwall in Sweden and with ours.

Case 6. This is a report of a recent experience in the treatment of a patient with severe uremia on the basis of a chronic nephritis.

A 30 year old truck driver with severe uremia was rushed to the hospital as an emergency case. He had worked until a week prior to admission; but further

investigation disclosed that he had been rejected from the Army for albuminuria many years previously, and hypertension was evident a year before admission. He had experienced impaired vision four weeks prior to admission, had suffered severe headaches since that time and had been vomiting for a week. He was extremely ill when he entered the Clinic. He dozed, and twitched continuously during questioning. The blood pressure was 210/130 mm. Hg. There was severe retinopathy and albuminuria.

He was treated with the artificial kidney. In 5 hours the blood urea was reduced from 309 to 186 mg. per hundred milliliters. Three days after the dialysis, the patient's clinical condition was improved. Since his progress was so satisfactory, he felt that one week of hospitalization was adequate. His daily urine output increased from 400 or 300 to 1300 and 1700 and 2000 ml. per 24 hours. He was started on a low-protein, high-caloric diet, and left the hospital satisfied but against our advice. A call from his doctor a week later informed us that he was progressing fairly well.

Several reports of patients whom we followed for many months or a year after they were given a new start with dialysis (specifically peritoneal lavage) have been published elsewhere (Kolff, 1952).

Intoxications without primary nephrotoxic actions. Intoxications with bromide, salicylate, and barbiturates may be treated with the artificial kidney even if uremia is not present. Barbiturates (Alwall, Lindgren and Lunderquist; Kyle, Jeghers, Walsh, Doolan, Wishinsky and Pallotta; Walsh, Kyle, Doolan and Jeghers); acetylsalicylic acid (Doolan, Walsh and Wishinsky).

Intractable edema as indication for treatment with the filtrating type of artificial kidney. The first purely filtrating type of artificial kidney was constructed by Malinow and Korzon (Kolff, 1950). It functioned by filtration only; there was no dialysis. Alwall's (Kolff, 1950) artificial kidney and Skeggs, Leonards and Heisler's artificial kidney can be used as a dialyzing and filtrating apparatus by simply putting negative pressure on the outflow of the rinsing fluid. It is hoped that MacNeill's kidney will also be usable in this way.

Intractable edema may occur in many clinical conditions. It often complicates acute or chronic uremia. Per hour, one liter of edema fluid can be removed by ultrafiltration. Hematocrit determinations must be done to avoid too rapid dehydration. As a relative oliguria often follows treatment with filtration, it is necessary to restrict the patient's fluid intake the following days. Sometimes, however, diuresis follows a single treatment with a filtrating artificial kidney. The following case is an example. This patient was treated at the Cleveland Clinic in co-operation with Leonards and Heisler using their stationary artificial kidney.

Case 7 (fig. 11). A 47 year old man was known to have polycystic kidneys for at least ten years. He had been maintained on a high-caloric, low-protein diet for 1½ years. He entered the Clinic September 25, 1952. Extensive edema was present. With digitalis, bedrest, low-sodium diet and mercuhydrin, his weight was reduced from 172 to 168 pounds. After that it was impossible to reduce it further. His blood urea varied from 186 to 222. The edema involved

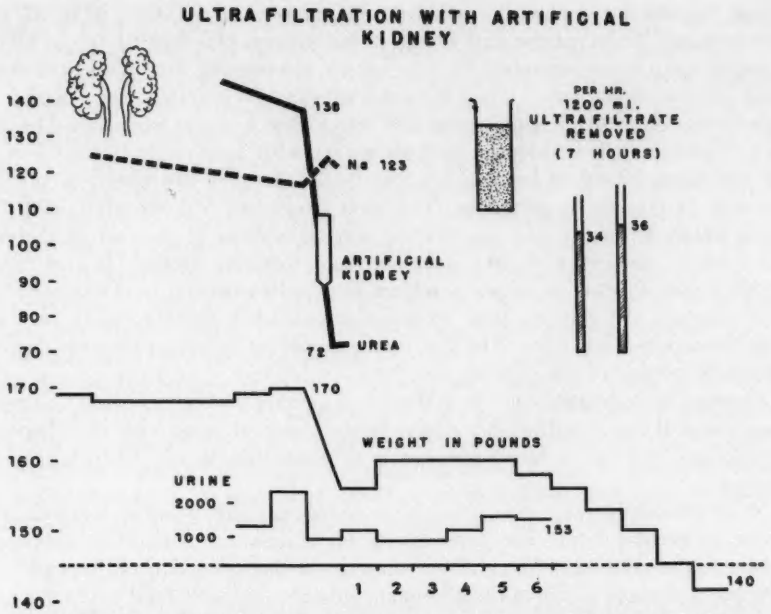


FIG. 11. Removal of "intractable" edema in patient with polycystic kidneys. Hematocrit reading increased from 34 to 36 per cent as indicated at right in figure.

the lower part of the body. There was ascites with a drum-like tension of the abdomen. He was treated with filtration and dialysis for 7 hours. The usual composition of rinsing fluid was used with 135 mEq of sodium per liter. During the day he was treated, he lost 13½ pounds of weight. It should be taken into account that he was transfused with 1100 cc of blood during the procedure. The amount of ultrafiltrate removed could be measured during the second half of the procedure and amounted to almost 1200 cc per hour. Towards the end of treatment, the patient enjoyed a ham sandwich allowed for the occasion. During 4 days following treatment with the artificial kidney, there was some increase in weight and of edema, but later, there was a steady decrease, and he left the hospital much improved and without edema.

DANGERS AND COMPLICATIONS OF TREATMENT WITH THE ARTIFICIAL KIDNEY

Heparin dosage, etc. The complications of treatment with the artificial kidney have been reviewed in earlier publications (Kolff, 1947). As Merrill has stated, these early problems have been overcome; hence, hemolysis, clotting and shock are rare with the apparatus if skillfully handled. With the use of new polyvinyl chloride tubing instead of rubber tubing for each patient and of course new, boiled cellophane tubing for each patient, pyrogenic reactions are practically eliminated.

1) *Hemorrhage.* With the use of polyvinyl chloride tubing and silicone coated

glass, the amount of heparin needed can be reduced. At the start, 80 to 100 mg. are required in the patient and 40 mg. in the kidney, plus 5 or 10 mg. to fill the arterial and venous cannulae. During dialysis, the clotting time is checked every half hour or every hour. When it is shorter than 20 minutes, more heparin is administered. Multiple small doses are better than a single large one. The aim is to maintain sufficient length of clotting time with hourly injections of 5 or 10 or sometimes 20 mg. of heparin. During the last hours of the dialysis a clotting time of 12 minutes is permitted. The total amount of heparin administered is from 100 to 200 mg. Often the clotting time is normal at the end of dialysis. As a result, the major danger of hemorrhage, formerly present, is now rarely encountered. Protamine sulfate is seldom required to neutralize the heparin. It will decrease the clotting time within a minute, but repeated injections are sometimes essential. (The bleeding time may persist in being prolonged despite return to normal of the clotting time.)

Cerebral hemorrhages have been described as complications (Fishman, Kroop, Leiter and Hyman), although we have never observed them. Once less heparin is used and the rise in blood pressure is avoided, this danger will probably be lessened.

With extremely poor management, it is theoretically possible for technical errors to become fatal. The patient may bleed into the distensible cellophane tubing in the rotating kidney if the outflow of the kidney is blocked, or a patient may bleed through a hole in the cellophane into the dialyzing fluid in the stationary kidneys. Such accidents have not happened yet, but the artificial kidneys need constant supervision.

2) *Hypertension.* When the blood flow through the apparatus is 200 ml. or more per minute, a rise in blood pressure is frequently observed, which is sometimes alarming. With lower flow rates it is rare. Neither the Boston group (Haynes, Merrill and Goodale) nor our own has been able to demonstrate the presence of pressor substances in blood after dialysis. The rise in blood pressure can, if necessary, be immediately reduced with hexamethonium or by draining 300 ml. of blood into a burette along the inflow of the artificial kidney. The flow rate should then be reduced. The rise in blood pressure, unwelcome as it is in most patients, has been used for treatment of otherwise refractory hypotension in patients with what is sometimes called irreversible shock (Merrill, Smith, Callahan and Thorn). Frank et al. however, have not been able to produce a rise in blood pressure with the artificial kidney in dogs with irreversible shock.

3) *Hemolysis.* A mild degree of hemolysis cannot always be prevented when the rotating type of kidney is used. Usually the hemolysis is barely visible but sometimes it is more evident. Unfortunate consequences so far have not been apparent.

4) *Relative urinary suppression.* In patients with chronic uremia, it may be observed that there is a diminished output of urine on the day of treatment with the artificial kidney and on the day following. Merrill and his co-workers (1953) added urea to the rinsing fluid and thus removed retention products except urea, and they observed no reduction of urine volume thereafter. They concluded that the reduction of the urea level in the blood was responsible for the diminished

diuresis. We are not convinced that this is the only explanation as the diuresis is usually restored before the blood urea has returned to its former height.

In patients with slow recovery of an acute urinary suppression. a similar temporary reduction of diuresis has sometimes been observed and caused more concern. Dr. P. Teschon has been able to prevent the relative oliguria by the addition of urea to the rinsing fluid in three patients with acute urinary suppression which again supports the view that the lowering of the blood urea is the cause. If, however, the relative oliguria were due to diminished renal blood flow, we might add injury to insult. It will be interesting to observe whether newer types of artificial kidneys will cause this temporary diminished urine output.

5) *Pulmonary complications.* Such incidents should not be listed as complications of the artificial kidney. On the contrary, they are usually greatly improved by dialysis both by combating pulmonary edema and by making the patient more alert so that he may cough. The employment of sedatives should be avoided as much as possible—codeine is forbidden. Often pneumonitis or poor expectoration with subsequent anoxia is responsible for death in debilitated patients with uremia. Tracheotomy followed by frequent aspiration should be performed more often and at an earlier period, but it may be very difficult to distinguish beginning pulmonary edema due to cardiac failure from stagnating secretions.

CONTRA-INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

Active uncontrollable bleeding is the only absolute contra-indication. Heparinization may activate gastro-intestinal hemorrhage which is not uncommon considering the frequency of ulcers, necrosis of mucosa and spontaneous small hemorrhages present in patients who die in uremia (Mason). Hemorrhages from the gastro-intestinal tract during or after treatment with the artificial kidney are rarely serious. One case which required transfusions has been mentioned before in this paper. In our experience there was another case of bleeding from the rectum in a patient with mercurial colitis controllable only with a large transfusion. In the presence of wounds not bleeding at the time of observation the problem is one of calculated risks.

OTHER DIALYZING METHODS: PERITONEAL LAVAGE AND INTESTINAL LAVAGE

To compare other dialyzing methods with the artificial kidney, Kop and Kolff (1947, 1951) have treated more than 20 patients with peritoneal lavage. Also Twiss and Kolff (1951) treated a series of patients with intestinal lavage. When such methods are casually employed by inexperienced physicians, they may be accidentally successful; but as a rule such attempts are disappointing and have therefore become discredited.

a) *Peritoneal lavage.* This method is a useful procedure. It has the advantage that almost no special equipment is required; but the rinsing fluid must be sterile and its chemical composition must be correct. Peritoneal lavage is not so effective in terms of clearance as the artificial kidney. A number of unpredictable factors are its main drawback. Among these are: uncertainty of outflow, possible distention, possible pain that may last for several days, impairment of respiration and

others. We have tried Grollman's (1951) intermittent peritoneal lavage and agree with Legrain and Merrill that in humans, if not in dogs, a continuous perfusion is preferable although not so simple.

The bladder must be empty. Under local anesthesia a trocar is inserted through the abdominal wall at a site corresponding with McBurney's point, but on the left side. The stylet is withdrawn and a snuggly fitting polyvinyl chloride tube, or rubber tube is inserted into the peritoneal cavity; the trocar is then withdrawn. One-and-one-half or two liters of rinsing fluid heated to body temperature are instilled into the peritoneal cavity. In the intermittent method one may attempt to remove the fluid through the same cannula after two hours. It however saves time and disappointment if a second tube is inserted in the right side, as soon as the abdomen is distended with rinsing fluid.

The electrolyte composition of the rinsing fluid is the same as for the artificial kidney but must be sterile and terramycin may be added, 25 mg. per liter.

Inflow and outflow are carefully recorded and a fluid balance is made. It must be assumed that during the procedure and at the end, 1 or 2 liters of rinsing fluid will remain in the peritoneal cavity. The rinsing fluid is made hypertonic to make up for the expected loss. The glucose added in the beginning is 2½ per cent and it is often necessary to increase it to 5, 7½ or 10 per cent. Resulting pain may be suppressed by addition of 5 cc of a 1 per cent solution of procain per liter. The flow should not be less than one liter per hour. All oral intake is withheld.

When adhesions or gaseous distension is present, the danger of perforating the intestine exists. If the tube is left in place, surgical repair is not difficult. In the absence of perforation, with the help of antibiotics, and if the dialysis is not prolonged for more than three days, the chance for fatal peritonitis is negligible. Peritoneal lavage requires great care, continuous supervision and experience, but even then overhydration, distension and respiratory difficulties can not always be avoided.

The indications are the same as for the artificial kidney. Best results may be expected in the dehydrated patient with little fat in the omentum and in the abdominal wall and when there is no immediate danger from potassium intoxication.

Recent abdominal operations, infections and distension are relative contraindications. Most impressive are the results obtained by Derot and Legrain. Edema can be removed by adding more glucose to the rinsing fluid (van den Bossche and Kolff; Grollman, Turner and McLean) as is shown in the following case:

Case 8 (fig. 12). A woman 35 years of age cleaned a rug with carbon tetrachloride on a warm day. On the thirteenth day after the inhalation of carbon tetrachloride, she was sent to the Cleveland Clinic. Urine output so far had been negligible. She arrived in the middle of the night; extreme cyanosis was noted; rales were present in both lungs; edema and air hunger were observed; and the abdomen was distended. The blood pressure was 130/70 but sometimes it dropped to under 100. A peritoneal lavage was started while the patient was in an oxygen

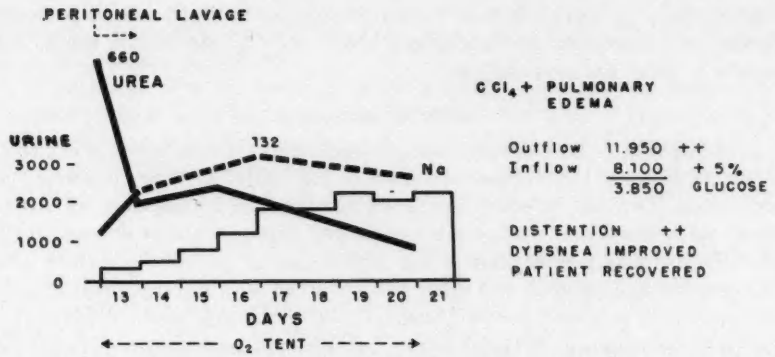


FIG. 12. Removal of edema in patient with CCl_4 poisoning and uremia by addition of 5 per cent glucose to rinsing fluid in peritoneal lavage.

tent. The electrolyte composition of the rinsing fluid was as follows: sodium 124; chlorides 104; calcium 4.5; potassium 1.3; magnesium 2.7; HCO_3' 20; HPO_4'' 1.8; lactate 6.7 mEq/L. Glucose was used in a concentration of 5.1 per cent. The inflow of the peritoneal fluid was 8.1 per liters; the outflow was 11.95. There were 3750 cc of fluid removed during approximately 10 hours of peritoneal lavage. The blood urea dropped from 680 to 300 mg. per cent. Sodium increased from 111 to 123. Potassium decreased somewhat from 6.8 to 6.3. The blood pressure the next morning was 150/80. It seemed that immediate danger caused by the pulmonary edema was subsiding. Treatment in the oxygen tent and antibiotics were continued. Fluid intake was restricted. The urine output gradually increased so that it reached 1500 cc on the nineteenth day of the intoxication. The following day she was removed from the oxygen tent. Potassium chloride had to be administered to avoid hypopotassemia. Her heart caused some difficulty with electrocardiographic changes, extrasystole and gallop rhythm, but eventually she made a complete recovery.

She was seen 6 months later, with a normal blood pressure, normal blood chemistry findings, urea clearance of 100 per cent in the first hour and 92 per cent in the second hour. There was no albumin in the urine and nothing abnormal in the sediment.

b) *Intestinal lavage.* Gastric and colonic lavage are inefficient in removing retention products like urea. Some potassium may be eliminated but it may be accomplished much better with the use of carboxylic resins. Dialysis through an isolated intestinal loop should not be attempted in the treatment of acute uremia, but may find a place in the treatment of chronic uremia. The seemingly simple dialysis using the entire intestinal tract is the most difficult of dialyses. The mucosa of the intestinal tract can be used as a dialyzing membrane, but it also is an active, absorbing, secreting organ. The composition of rinsing fluid is entirely different from that used for peritoneal lavage or artificial kidney (Kolff, 1951; Twiss). With the patient, bed and all, on a scale, with a hole in the bed to

drain feces due to inevitable diarrhea and leakage, and with frequently performed electrolyte determinations, Hamburger, Mathe and Crosnier obtain results comparable to other forms of dialysis.

FUTURE OUTLOOK

In the light of present development, it seems that artificial kidneys will retain or further establish for themselves a place in the treatment of acute uremia. It is hoped that they will be more frequently used in the management of chronic uremia to induce a new start, a more prolonged improvement or at least to alleviate the distressing symptoms of the chronic uremic patient for a short time. Conservative management will make further progress in the treatment of acute and chronic uremia with better understanding of the fluid and electrolyte balance, with development of better resins that will bind large amounts of retention products, and with the development of better methods of feeding these patients intravenously or by other methods. The time is not far that we will write to the referring doctor a letter which reads like this: "Your patient, Mr. Jones, was sent home today. He should take a high-caloric, 20-gm. protein diet which may be supplemented with oral fat emulsion. He should take a combination of sodium-binding and potassium-binding resin to permit a normal sodium intake with the diet, and to maintain his potassium at the right level. These two resins will also sufficiently remove retention products. If he takes three tablets of a methyl cellulose compound, he will bind sufficient water in his intestinal tract to allow a fluid intake of two liters per day. A new type of hydrazinophthalazine takes care of the hypertension. About his kidneys, you will not have to bother as we have removed both of them."

SUMMARY

It is possible to save the life of the majority of patients with acute urinary suppression with so-called conservative treatment, but it may be difficult; and when it fails dialysis still offers a chance. While immediate improvement is often obvious and life can be prolonged, there is little statistical proof as yet that use of the artificial kidney increases the number of ultimate survivers.

The general principles of the treatment of uremia are the following:

1) Control of water and electrolytes.

2) Suppression of protein catabolism with forced, high-caloric, low-protein diet.

3) Avoidance and treatment of infections.

4) Removal of retention products and the correction of body electrolytes with dialyzing methods.

There are three types of artificial kidneys: 1) artificial kidneys using dialysis without filtration (Kolff rotating type); 2) artificial kidneys using dialysis plus filtration (Skeggs, Leonards and Heisler artificial kidney and most other types); and 3) resin artificial kidneys. Rinsing fluid should contain less sodium than the normal content of extracellular fluid, otherwise too rapid correction from low to normal levels may occur. Extra glucose may be added to make the rinsing fluid

hypertonic to aid in removing edema. However, it is more effective to use a filtering-type artificial kidney.

The treatment of acute uremia with the artificial kidney varies. Some prefer treatment early in order to prevent the discomfort and dangers of uremia, especially in older people. Others postpone dialysis until the blood urea approaches 300 mg. per cent, the serum potassium reaches 7 mEq per liter and the alkali reserve is lower than 12 mEq per liter, or the patient's clinical condition deteriorates.

It may be worthwhile to give patients with chronic uremia the benefit of one treatment with the artificial kidney since approximately one third of such patients may have an improvement in their clinical condition that lasts for an average of two months. The dangers of treatment with the artificial kidney in experienced hands are minimal. The occurrence of hemorrhage has been greatly reduced since the heparin dosage used is from 100 to 200 mg.

Peritoneal lavage using a simplified technique with trocars is effective, but complications are unpredictable. Intestinal lavage, although seemingly simple, is the most difficult of all dialyses, but with great care, optimum facilities and frequent control of blood electrolytes, its results may compete with the artificial kidney and peritoneal lavage. The use of any dialyzing method outside a center with special facilities for that particular method is discouraged.

REFERENCES

Abel, J. J., Rowntree, L. G. and Turner, B. B.: On the removal of diffusible substances from the circulating blood of living animals by dialysis. J. Pharmacol. & Exper. Therap., **5:** 275, 1913–1914.

Alwall, N., Lindgren, P. and Lunderquist, A.: On artificial kidney XX. Treatment of severe phenobarbital poisoning in rabbits, by means of forced polyuria, exchange ultrafiltration and dialysis, and a preliminary report on dialytic treatment of barbiturate poisoning in patients. Acta med. Scandinav. **143:** 299, 1952.

Bull, G. M., Joekes, A. M. and Lowe, K. G.: Conservative treatment of anuric uraemia. Lancet, **2:** 229, 1949.

Derot, M. and Legrain, M. in: Tzanck, A., Derot, M., and others: Traitement des néphrites aiguës anuriques par les méthodes d'épuration extra-rénale. Monographies du Centre national de transfusion sanguine. Masson, Paris, 1951.

Doolan, P. D., Walsh, W. P., Kyle, L. H. and Wishinsky, H.: Acetylsalicylic acid intoxication, a proposed method of treatment. J.A.M.A., **146:** 105, 1951.

Fishman, A. P., Kroop, I. G., Leiter, H. E. and Hyman, A.: Experiences with Kolff artificial kidney. Am. J. Med. **7:** 15, 1949.

Frank, Howard A., Frank, Edward D., Jacob, S., Glotzer, P., Persky, L., Friedman, E. W., Schwartz, A., Rutenburg, A. M., Milrod, S. and Fine, J.: Traumatic shock. XX. The course of hemorrhagic shock in dogs treated by peritoneal irrigation or by artificial kidney. Am. J. Physiol., **168:** 140, 1952.

Goldner, F., Gordon, G. L. and Danzig, L. E.: The use of the artificial kidney in chronic renal disease. A.M.A. Arch. Int. Med.; **93:** 61, 1954 .

Grollman, A., Muirhead, E. E. and Vanatta, J.: Role of kidney in pathogenesis of hypertension as determined by a study of the effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog. Am. J. Physiol., **157:** 21, 1949.

Grollman, A., Turner, L. B. and McLean, J. A.: Intermittent peritoneal lavage in nephrectomized dogs and its application to the human being. A.M.A. Arch. Int. Med., **87:** 379, 1951.

Guarino, J. R. and Guarino, L. J.: An artificial kidney—a simplified apparatus. Science, **115:** 285, 1952.

Hamburger, J., Mathe, G. and Crosnier, J.: La perfusion intestinale dans le traitement de l'insuffisance rénale aiguë. Bull. et mém. Sôc. méd. hop. Paris **66:** 1716, 1950.

HAYNES, F. W., MERRILL, J. P. AND GOODALE, W. T.: Plasma renin concentration of patients treated with artificial kidney. Fed. Proc., **11:** 67, 1952.

HOUCK, C. R.: Problems in maintenance of chronic bilaterally nephrectomized dog. Am. J. Physiol. **176:** 175, 1954.

HOUCK, C. R.: Effect of hydration and dehydration on hypertension in chronic bilaterally nephrectomized dog. Am. J. Physiol. **176:** 183, 1954.

KOLFF, W. J.: New Ways of Treating Uraemia: The Artificial Kidney, Peritoneal Lavage, Intestinal Lavage. London: J. & A. Churchill, Ltd., 1947, 112 pp.

KOLFF, W. J.: Artificial kidney; treatment of acute and chronic uremia. Cleveland Clin. Quart. **17:** 216, 1950.

KOLFF, W. J.: Forced high caloric, low protein diet and the treatment of uremia. Am. J. Med., **12:** 667, 1952.

KOLFF, W. J.: Treatment of uremia; use and indications for high caloric low protein diet, dialyzing methods and replacement transfusion. Cleveland Clin. Quart. **18:** 145, 1951.

KOLFF, W. J. AND FISHER, E. R.: Pathologic changes after bilateral nephrectomy in dogs and rats. Lab. Investigation, **1:** 351, 1952.

KOP, P. S. M.: Peritoneal dialysis. Kampen, Holland: J. H. Kok. N. V., 1948, 220 pp.

KYLE, L. H., JEGHERS, H., WALSH, W. P., DOOLAN, P. D., WISHINSKY, H. AND PALLOTTA, A.: The application of hemodialysis to the treatment of barbiturate poisoning. J. Clin. Investigation, **32:** 364, 1953.

LEONARDS, J. R. AND HEISLER, C. R.: Artificial kidney. IV. Maintenance of life in bilaterally nephrectomized dogs and its relation to malignant hypertension. Am. J. Physiol., **167:** 553, 1951.

LEGRAIN, M. AND MERRILL, J. P.: Short-term continuous transperitoneal dialysis: Simplified technic. New England J. Med., **248:** 125, 1953.

LEWIS, F. J., REISER, M. P., EGDAHL, R. H., RAFFUCCI, F. L. AND FLINK, E. B.: Clinical uses of the artificial kidney. Journal-Lancet, **72:** 1, 1952.

MASON, E. E.: Gastrointestinal lesions occurring in uremia. Ann. Int. Med., **37:** 96, 1952.

MERRILL, J. P.: Medical progress; artificial kidney. N. Eng. J. Med., **246:** 17, 1952.[a]

MERRILL, J. P.: The use of the artificial kidney in the treatment of uremia. Bull. New York Acad. Med., **28:** 523, 1952.[b]

MERRILL, J. P., LEGRAIN, M. AND HOIGNE, R.: Observations on role of urea in uremia. Research Society Abstracts, American Federation for Clinical Research, Am. J. Med. **14:** 519, 1953.

MERRILL, J. P., SMITH, S., III, CALLAHAN, E. J., III AND THORN, G. W.: Use of artificial kidney; clinical experience. J. Clin. Investigation, **29:** 425, 1950.

MERRILL, J. P. AND WELLER, J. M.: Treatment of bromism with the artificial kidney. Ann. Int. Med., **37:** 186, 1952.

MUIRHEAD, E. E., VANATTA, J. AND GROLLMAN, A.: Acute renal insufficiency; comparison of use of an artificial kidney, peritoneal lavage and more conservative measures in its management. Arch. Int. Med. **83:** 528, 1949.

MURPHY, W. P., JR., SWAN, R. C., JR., WALTER, C. W., WELLER, J. M. AND MERRILL, J. P.: Use of an artificial kidney. III. Current procedures in clinical hemodialysis. J. Lab. & Clin. Med., **40:** 436, 1952.

OLIVER, J., MACDOWELL, M. AND TRACY, A.: The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and ischemuric episode. J. Clin. Investigation, **30:** 1307, 1951.

SKEGGS, L. T., JR., LEONARDS, J. R. AND HEISLER, C. R.: Artificial kidney II. Construction and operation of an improved continuous dialyzer. Proc. Soc. Exper. Biol. & Med., **72:** 539, 1949.

SNAPPER, I.: On extracorporeal dialysis in blood in acute anuria; the importance of β-oxidation in the kidney tubules. Bull. New York Acad. Med., **28:** 621, 1952.

STOCK, R. J.: The conservative management of acute urinary suppression. Bull. New York Acad. Med., **28:** 507, 1952.

TWISS, E. E.: Treatment of uremia by dialysis and other methods with special regard to the principles and scope of intestinal dialysis. Rotterdam, Holland: M. Wyt and Sons, 1950, 208 pp.

VAN DEN BOSSCHE, M. AND KOLFF, W. J.: Possible removal of edemic fluids by dialysis with hypertonic glucose solution. Geneesk. gids, **26:** 284, 1948.

WALSH, W. P., KYLE, L. H., DOOLAN, P. D. AND JEGHERR, H. J.: Treatment of barbiturate poisoning by hemodialysis. Am. J. Med., **13:** 104, 1952.

WOLF, A. V.: The artificial kidney. Science, **115:** 193, 1952.

WOLF, A. V., REMP, D. G., KILEY, J. E. AND CURRIE, G. D.: Artificial kidney function: kinetics of hemodialysis. J. Clin. Investigation, **30:** 1062, 1951.

DISCUSSION

DR. REED M. NESBIT (Ann Arbor, Mich.): To discuss these papers would be not only presumptuous but gratuitous. However, I would like to talk for one moment about one thing that hasn't been mentioned, and that is "catching the rabbit." You know, there is an old story about a certain recipe that started off with "First, catch your rabbit."

One of the greatest difficulties in the management of oliguria is early discovery. The blood chemistry studies, which sometimes take a long period of time, do not give us a diagnosis. How, then, can we make a diagnosis in a patient who has been operated upon recently or who has been brought into the hospital just a few moments before, and who is known to be oliguric? How can we determine immediately what course of events we can put into effect in the management of the patient?

The simplest test that I know that a urologist can carry out is usually the one nobody has thought of, and that is a study of the specific gravity of the urine. That was mentioned by one of the essayists this morning. I simply want to emphasize the urgent necessity of making that one observation immediately when the question arises, because nearly every oliguric patient who is suffering from true oliguria has urine that has a specific gravity of 1.010 or 1.012 or 1.014, and the observation of this one point is essential and very helpful to us as teachers and as consultants.

DR. DAVID M. DAVIS (Philadelphia, Pa): I have been struck for a long time with the fact that in the course of these immensely careful and detailed studies of renal function—in which it would seem that every possible factor has been built into the intellectual concept and from that intellectual concept into the plan of research and investigation—there is one factor that has been very largely neglected, and I believe it is of absolutely fundamental importance.

In Dr. MacLean's paper, as you will recall, he spoke of the blood pressure, the blood flow through the kidney, the composition of the blood, and numerous other factors. The one factor which has not been considered in most of the excellent work that has been done is the effect upon renal function of changes in the intrapelvic pressure.

Intrapelvic pressure might be regarded as a function of the efficacy of the conducting part of the urinary tract.

Dr. Leadbetter has spoken of obstruction. That, however, is a thoroughly relative term. It means different things to different people. I think if we were to concentrate, rather on the concept of alterations in the intrapelvic pressure, we needn't concern ourselves so much with what causes those alterations.

This is a very difficult subject, because there is no good or even satisfactory method of measuring the intrapelvic pressure, either clinically or experimentally, in cases where it is normal or where it is abnormal. Therefore, we do not know what the normal pressure conditions in the human renal pelvis are—we have to guess at what they are; oftentimes we do not even know when abnormal conditions

exist. The only method we have of telling anything about it is to take a pyelogram.

The pyelogram, of course, is just a picture of a form, and it shows only those situations in which the mechanisms of the renal pelvis which enable it to compensate to a certain degree against obstruction, or stenosis in the conducting channels, have been overcome, and there is a state of decompensation. Then, and only then, does pyelectasis of a degree demonstrable in x-ray films begin.

The important thing is for someone to discover an adequate and practical method—which I doubt not can be done by some of our men who are familiar with modern physics—of measuring the intrapelvic pressure. Then we will know in what cases the intrapelvic pressure is too high; we can restore it to normal by proper surgical procedures, and we can see for ourselves just how much good this accomplishes.

Dr. Wyland F. Leadbetter (Boston, Mass.): I have enjoyed very much listening to these papers. It seems to me they give a pretty well-rounded idea of what is going on today in this field in Urology, which is so important.

Dr. Samuel A. Vest (Charlottesville, Va.): I was very much interested in the pelvic pressure mentioned by Dr. Davis. At our institution we have been more interested in total intrarenal pressure.

One of my assistant residents has been working on this subject. Mr. Frederick J. Wallace of American Cystoscope Makers, Inc. devised for us a tiny rubber bag which is attached to the end of a ureteral catheter for measuring the pressure inside the renal capsule. We do this by making a tiny slit in the capsule near the lower pole and then slide the bag up between the inelastic capsule and the outer surface of the kidney. The bag is long and narrow in contour and it is inserted practically to the upper pole of the kidney beneath the capsule. It is then inflated and by measuring the pressure inside the rubber bag we are able to record the pressure inside the renal capsule. Any changes in the size of the renal parenchyma according to blood flow results in changes in intracapsular pressure which we assume to be the same as intrarenal pressure. We simultaneously measure the carotid blood pressure directly. Using this method we hope to undertake to do various experiments on toxicity and possibly throw some light on the etiology or mechanism of lower nephron nephrosis.

I certainly enjoyed the talks, especially that by Dr. Kolff. I know that you will recall that it was due to his stimulus that the first artificial kidney was brought to this country a number of years ago. It was exhibited at a New York meeting and from this kidney there have grown the other kidneys that are in use today in Boston and other cities.

I certainly agree with Dr. Kolff that one can put too much emphasis on trying to correct low sodium concentrations in anuric patients. I did not mean to give the impression in my discussion on electrolytes that we always try to bring the sodium back entirely to normal. We only try to correct wide swings on variations in sodium concentration when we encounter it. We do not try to treat the acidosis in uremia unless the lungs are no longer able to compensate and they get into respiratory distress. Because if we do this by injecting too much sodium then

we have to pay the price of expanding the extracellular and plasma volumes, and we agree that that is unwise.

Just one thing about peritoneal lavage mentioned by Dr. Kolff. We have been interested in this subject and have had far better luck with one tube rather than the dual system of ingress-egress. When two tubes are used, one on each side of the abdomen, the fluid tends to form a channel among the intestines and one does not lavage a wide area of peritoneum. We recently reported a lavage in one patient in which 80 liters of fluid were injected into the peritoneal cavity over a period of nine days and we got back exactly 80 liters. We believe this was due to the use of one tube and to a proper solution which we devised. We measured the osmotic pressure by the freezing point depression and constructed a solution which was near that of the blood pressure so that we would have no volume change whatever. By the injection of such a fluid and then turning the patient in bed it was distributed over the peritoneal cavity and we recovered the exact amount injected without any loss or gain.

BILATERAL CONCOMITANT SEMINOMA

A. I. DODSON AND J. W. HOOPER, JR.

From the Department of Urology of the Medical College of Virginia, Richmond, Va.

Concomitant malignant testicular tumors in normally placed testicles are rare. There is not a case in the Tumor Registry of the Army Institute of Pathology at Washington, D. C. Hamilton and Gilbert[1] analyzed 7,000 case records of testicular tumors and found 134 cases in which each testicle was involved in cancer at some time. These cases were not of simultaneous involvement and frequently months and years elapsed between involvement of the remaining testicle after removal of the other, thus not ruling out metastasis. In 1949, Hotchkiss and Laury[2] in reviewing the medical literature to the year 1805 were able to find only 21 cases and reported one of their own. Since this review one additional case[3] has been added which, with the case to be reported, brings the total number of cases to twenty-four. If an analysis of the cases of concomitant involvement of the testicles by malignant tumor is further studied it is found that of the 23 cases reported only twelve fall into the classification of primary testicular malignancy as described by Moore or interstitial cell tumor with the remaining cases being of lymphoid or sarcomatous origin. Of the twelve patients with primary testicular tumors six are of embryonal carcinoma,[4, 5, 6, 7, 8, 9] two of encephaloid tumor,[10, 11] type indiscernible, two of interstitial cell tumor,[3, 12] one of carcinomatous teratoma,[13] and one of adenocarcinoma.[14] The case to be reported brings the total number of bilateral primary testicular tumors in normally placed testicles to thirteen.

This is the first case of bilateral seminoma arising concomitantly in normally placed testicles. The patient is living 32 months following treatment with no evidence of disease, which is unusual. He maintains normal libido in the absence of both testicles. Emphasis should be placed on earlier diagnosis of testicular malignancy by considering any mass adjacent to the testicles malignant until proved otherwise. In this case five physicians examined the patient and not one suspected malignancy.

CASE REPORT

J. C. D., a 40 year old white male railroad conductor, was admitted to the Medical College of Virginia Hospital on July 17, 1950, with a chief complaint of

[1] Hamilton, J. B. and Gilbert J. B.: Cancer Research, **2**: 125–129, 1942.
[2] Hotchkiss, R. S. and Laury, R. B.: J. Urol., **63**: 1086–1092, 1950.
[3] Garvey, F. K. and Daniel, T. B.: J. Urol., **66**: 713–719, 1951.
[4] Higgins, C. C.: Ann. Surg., **88**: 242–247, 1928.
[5] Venable, J. M. and Flynt, S. P.: J. Urol., **26**: 155–158, 1931.
[6] Pierson, E. L., Jr.: J. Urol., **28**: 353–363, 1932.
[7] Graves, R. C. and Lawrence, K. B.: J. Urol., **37**: 482–490, 1942.
[8] Smith, G. C.: J. Urol., **50**: 585–589, 1943.
[9] Gill, R. D. and Newell, R. B.: J. Urol., **59**: 940–947, 1948.
[10] Bidard, M.: Bull. Soc. anat. de Paris, **28**: 345–346, 1853.
[11] DeLaunay, M.: Bull. Soc. anat. de Paris, **35**: 273–277, 1860.
[12] Kaufman, E.: Verhandl. deutsche Path. Gesellsch. Med., **11**: 237–250, 1907.
[13] Tanner, C. C.: Calif. State J. Med., **21**: 55–56, 1923.
[14] Lewis, E. B. and Priestley, J. T.: Proc. Staff Meet. Mayo Clinic, **13**: 737–740, 1938.

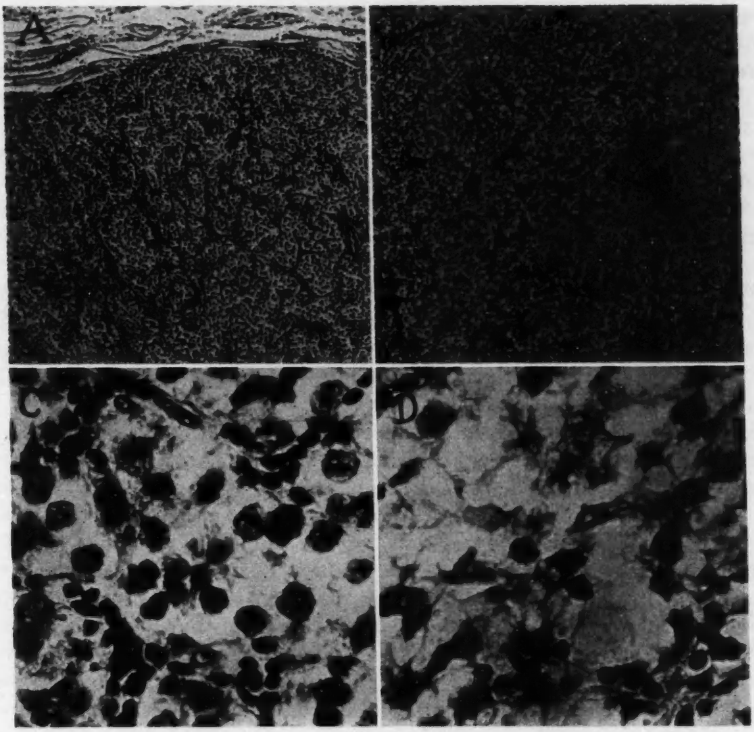


FIG. 1

"swollen testicles" for 6 months. Six months prior to admission the patient was seen by a local physician for swelling of the left testicle and at this time swelling at the base of both testicles was detected with hardness and induration. He gave no history of gonorrhea, stricture, or prostatism and had no urinary symptoms. The patient had had no chills and no fever with no weight loss, and there was nothing in the history to suggest tuberculosis. The patient was given penicillin therapy and sitz baths periodically with no improvement, and because the testicular swelling increased with more hardening but little pain he was admitted to this hospital.

Laboratory examinations revealed nonprotein nitrogen 28, hemoglobin 14, with 4,800,000 red blood cells and a white count of 7,300 with a normal differential. The urine was normal, the Wassermann test negative, and a chest film was within normal limits.

Physical examination revealed a well-developed, well-nourished man lying comfortably in bed not appearing acutely nor chronically ill. The temperature was 98.4, pulse 82, respirations 20, and blood pressure 120/80. The positive physical findings were limited to the genitalia. Both testicles felt normal except in the region of the power pole, which was poorly defined and could not be dis-

tinguished from the head of the epididymis which was felt to be thickened on both sides. Both vasa felt normal. The preoperative diagnosis was bilateral chronic epididymitis and the patient scheduled for bilateral epididymectomy.

The testicles were exposed through curved incisions beginning on either side at the external ring and extending down into the scrotum. The testicles revealed a whitish, rounded, firm lesion at either lower pole with fibrosis of the adjacent epididymis. Neither testicle was grossly enlarged. A frozen section was done on each testicle and the diagnosis was seminoma. Following this, bilateral orchiectomy was carried out by ligating each spermatic cord and adjacent structures in turn high in the inguinal canal. The wounds were closed in layers.

Pathological report: Grossly the right testicle measured 4 by 4 by 1½ cm. and the left 3½ by 3½ by 1½ cm. Both testicles at the lower pole adjacent to the epididymis showed a grayish white tumor measuring 1 by 1 by 1½ cm. and displacing the testicular tissue. The epididymides showed some thickening bilaterally.

Microscopic and histological appearance revealed an identical picture in sections of the right and left testes (fig. 1, *A* and *B*). This comprised a tumor made up of polyhydral and rounded cells of uniform arrangement (fig. 1, *C* and *D*). Formations of alveolar configurations separated by collagenous stroma were seen. No acini were evident. There was slight variability in the size of the cells. For the most part, the cell borders were distinct and delineated abundant cytoplasm with clear or faintly granular cytoplasm. In some of the tumor cells the cytoplasm had a reticular appearance. The nuclei were distinctive, being uniform, round or oval, and centrally placed. Tumor giant cell formations were rarely seen. In the typical neoplastic cell the nuclear chromatin filaments or granules were evenly dispersed and varied somewhat in amount from one cell to the other. The majority of the cells contained one prominent nucleolus but two or three such structures were frequent. Pathological or heterotype mitoses were abundant. Practically all of the cells were hyperchromatic.

The stroma in section from both testes was abundant, consisting of dense bands of collagen and reticulum embedded in which were numerous lymphocytes or lymphoid cells. Occasionally lymphoid follicles with germinal centers were obvious. Plasma cells and eosinophilic granulocytes also contributed to the stromal cellular content.

No multinucleated giant cells of the foreign body types were seen. "Epithelioid" cells were absent. The vascularity appeared to be confined to the capillaries running in the connective tissue stromal bands.

The seminiferous tubules adjacent to the tumor mass showed some atrophy. At a distance, however, they were preserved and revealed active spermatogenesis. Atrophic tubules were seen here and there within the tumor. The epididymides appeared free of involvement. Diagnosis: Seminoma of the testes, bilateral (Gordon R. Hennigar, M.D.).

Postoperatively the patient received an average of 2000 roentgens to the lumbosacral area, the aortic nodes, and the mediastinum up to and including cervical seven. This was delivered through multiple ports 10 by 20 cm. in size

at a 50 cm. distance using 200 K.V., 20 milliamperes and ½ cm. of copper over a period of 20 days. When last heard from, 32 months following completion of treatment, the patient was living and well with no evidence of tumor and maintaining normal libido.

SUMMARY

The first recorded case of bilateral seminoma is presented which occurred concomitantly in both testicles. Following bilateral orchiectomy and x-ray therapy the patient is living and well 32 months with no evidence of disease and no impairment in potency. The importance of considering all masses in the scrotum, particularly those adjacent to the testicle, as malignant until proved otherwise is emphasized.

409 Medical Arts Bldg., Richmond 19, Va.

A TRUE HERMAPHRODITE

ARTHUR B. CECIL

Since the founding of this Association in 1886, only 2 cases of true hermaphroditism have been reported before it. These two cases were reported in a paper by Kiefer and McKenna in 1944. The condition of rarity alone, however, would not prompt me to present this subject to you. I have decided to do so because I wish to discuss some original ideas in regard to the surgical treatment of intersexuality.

A. D. 0-7161, aged 6, who had been raised as a boy, was admitted to the Hospital of the Good Samaritan in Los Angeles, California, on December 2, 1935. The case was considered one of male pseudohermaphroditism. The penis showed ventral curvature, below which was a groove running into a urogenital sinus. There was no scrotum, nor could testicles be palpated. At this admission to the hospital a first-stage hypospadias operation was done for straightening of the penis.

The patient was lost sight of for 13 years, and was again admitted to the hospital of the Good Samaritan on August 17, 1948, at which time he was 19 years old (H.G.S. No. B.B. 8080). He had graduated from high school and had lived as a boy. The family history showed that he had four brothers: 24, 22, 17 and 15, and one sister, 21, all living and well and normally formed as were his father and mother.

When patient was 13 years old, and again 5 months previous to this admission, he had had vaginal bleeding. The first time the bleeding lasted for 1 week, and the second time for 3 days. He had male inclinations and desires, but had never had intercourse. He was most insistent that he be constructed as a male. Physical examination showed an individual weighing 140 pounds, 5 feet 6 inches tall. The general contour was that of a female: the breasts fairly large, the nipples highly developed with pigmentation about them. The pubic hair was of female distribution. There was no beard (fig. 1, *A*).

The phallus was 4.5 cm. in length and 2.5 cm. in diameter. The ventral curvature had been cured by the previous operation. There was a dimple representing a glandular meatus. On the ventral surface was a moist area running down to the urogenital sinus. On each side of this groove were labia minora 4 cm. in length (fig. 1, *B*). Just outside of the external ring one could palpate a mass which was about 2.5 cm. in its largest diameter. This was thought to be an undescended testicle. Nothing was made out in the left groin, and no hernia was present on either side. On rectal examination one could palpate a small body which was probably a uterus. A vaginogram showed a capacious vagina and a filling of the uterus and tubes (fig. 2).

On August 28, 1948, I excised the labia minora and did a Thiersch operation for the development of a urethra from the glans penis to the urogenital sinus, leaving the patient to urinate through the urogenital sinus. This operation was entirely successful (fig. 3).

FIG. 1

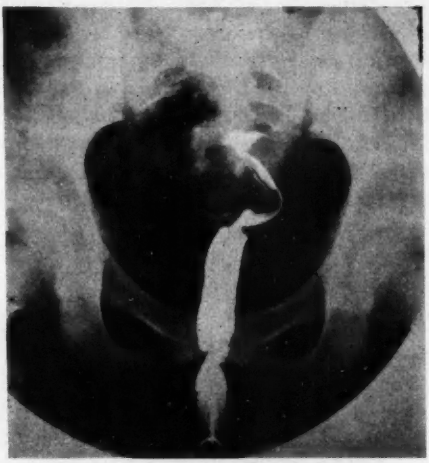


FIG. 2

On November 29, 1948, abdominal and right groin exploratory operations were carried out by Dr. Kenneth Blake and Dr. Arthur Cecil:

Total hysterectomy with bilateral oophorectomy and left salpingectomy; exploration of mass in the right groin: Upon opening the abdomen the uterus was smaller than one would find in a female 19 years of age. On the left side was a cystic ovary which measured 4 cm. in diameter. Lying above this was the left fallopian tube with its fimbriated end. This cystic mass and left tube were removed. The right tube was found to extend out into the right inguinal canal, and upon teasing it out with forceps, the fimbriated end was made out, but the tube could not be pulled into the abdominal cavity. The uterus was removed just below the cervix. After peritonealization, the abdomen was closed. An incision

FIG. 3

was now made over the mass in the right groin. The tunica vaginalis was opened, and within it was found a most remarkable organ. A rounded mass 2.5 by 2 cm. was located. The lower pole, which made up half of the mass, was of a grayish color, and the upper pole showed ovarian follicles. There was a definite line of demarcation between these two bodies. Biopsy specimens were taken from both poles and immediately studied by Dr. John Tragerman. The lower pole proved to be a testicle, and the upper pole an ovary. The biopsy opening of the testicle was closed and the ovarian tissue dissected loose from the testicle and removed. The tube was left in because of fear of interfering with the blood supply to the testicle. No attempt was made to change the position of the testicle.

Pathological report (Dr. John Tragerman): "Uterus and cervix are removed together in a slender mass 8.5 by 3.8 by 2 cm. (fig. 4). The fundus is thin and soft showing considerable serosal congestion. The top of the fundus is slightly concave. The cervix is elongated measuring 3 by 2.1 by 1.8 cm. The lower uterine segment is also rather slender. The uterus and cervix are widely opened. The

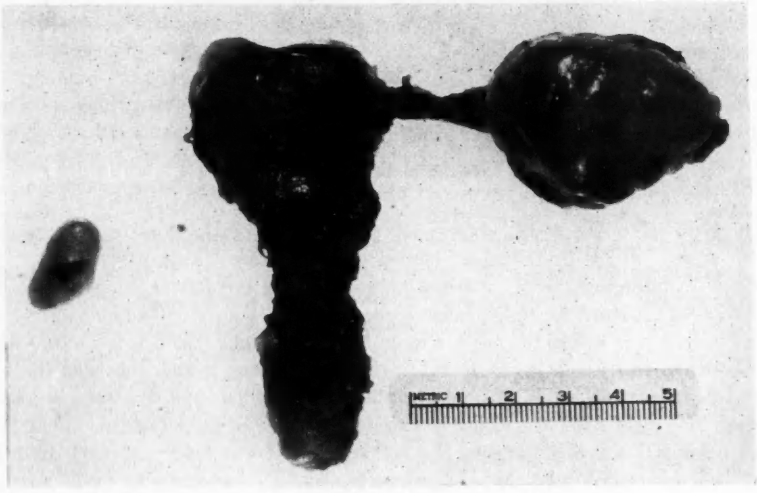


FIG. 4

walls vary in thickness. The cervix shows a rather wide canal containing a few transverse corrugations and several mucous cysts. A cord-like band of pale tissue extends from one wall of the internal os upward for about 1.5 cm., and then seems to become incorporated with the endometrium above. The endometrium is less than 1 mm. thick, showing a number of small areas of hemorrhage. The cord-like tissue is nearly 3 mm. in diameter. A block is taken from the uterine wall, at each end of the cord and also from one cornu, where a firm 5 mm. nodule is somewhat suggestive of adenomyoma.

"Microscopic: The uterus shows a rather compact muscle and is lined by a thin irregular endometrium somewhat atrophic in appearance. The nodule in the cornu is suggestive of a small myoma but no glandular structures are present. A block from the internal os shows numerous mucous glands, a few of which are distended. There is also a deeper zone in the tissue containing glands and cysts more like those of the endometrium. The termination of the cord-like structure described grossly shows a projecting nodule of uterine muscle surrounded by a thin inactive layer of endometrium, as already noted. Anatomical diagnosis:—atrophic endometrium. Nabothian cysts of endocervix.

"Left tube and ovary are removed together, the tube measuring 5.5 by .6 mm. The serosa is smooth but quite congested. The tube is slender and tortuous. The distal end is patent. The ovary is a collapsed oval cyst 4.3 by 3.2 by 1 cm. (fig. 4). It has been widely incised through the lower border showing a smooth lined cavity presenting a gray red membrane streaked with congested vessels. A few small yellowish plaques appear in the lining and in the cyst wall. Several flattened follicular cysts of varying size are present in the cyst wall. A block is taken from the wall near the pole.

"Microscopic: The stroma is fairly dense, containing numerous primitive ova, a small follicular cyst and an organizing corpus albicans and a regressing corpus luteum. One field, however, indicates that there are some follicular cysts lining the large cavity. Anatomical diagnosis:—follicular cysts of left ovary.

"Sections A and B are from the right inguinal mass suspected as ovotestis. Section A, from upper pole of right inguinal mass, shows dense ovarian stroma containing numerous primitive ova and part of the lining of a partly collapsed follicular cyst (fig. 5, *A*). Section B shows a group of tubular structures supported by a rather hemorrhagic stroma. Along one surface is a narrow zone of fairly dense fibrous tissue. The cells in the tubules show considerable variation—some are large with granular eosinophilic cytoplasm, others show clear cytoplasm and eccentric nuclei with some tendency to rest near the basement membrane. Other tubules, however, are diffusely filled with similar cells and there is little suggestion of an acinal lumen. The appearance is that of an undeveloped testicle (fig. 5, *B*)."

December 29, 1948, third-stage hypospadias operation, Cecil: Suprapubic drainage was done, and an elliptical incision was made around the opening of the distal urethra and the urogenital sinus. This opening was closed in layers. On the eighth day the suprapubic drainage tube was removed, and at the next urination patient urinated through the urethra in the normal fashion (fig. 6).

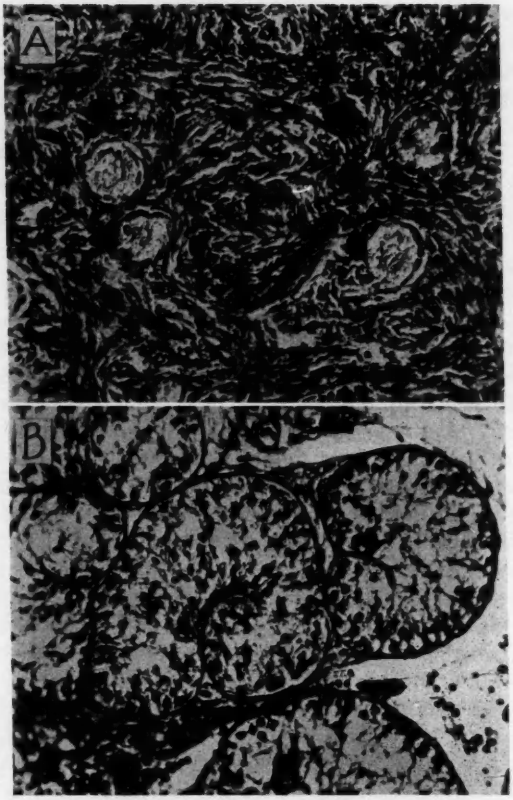


FIG. 5

The final stage in the male construction of this patient was the amputation of the breasts which was done by Dr. Kenneth Blake.

In 1942, Severinghaus[1] reported a study of the chromosomes of an intersex. In this case the secondary sex characteristics were a combination of male and female types. Exploration proved that the patient was a male pseudohermaphrodite. Biopsy specimens of the testicles were studied. The chromosomal content of the cells was found to be normal and the sex chromosomes corresponded with the gonadal sex. No studies of the chromosomal content of a true hermaphrodite have been made. Hooks[2] has given a splendid review of the literature dealing with sex determination, sex differentiation, and the effects of hormones on sex. It would be superfluous to further discuss this subject here.

I shall now take up the treatment of intersexuality which is more particularly in our field of endeavour. I have previously advocated that this treatment should

[1] Severinghaus, A. E.: Am. J. Anat., **70:** 73–87, 1942.
[2] Hooks, C. A.: J. Urol., **62:** 528–534, 1949.

FIG. 6

begin on the day of the birth of any individual whose sex is in doubt.[3] It is unfortunate that at the present time the only method by which gonadal sex can be determined is by exploration and biopsy of the gonads. As far as determining the gonadal sex is concerned, no cystoscopic, endoscopic or x-ray study is of any value whatsoever. Coffey did uretero-intestinal anastomoses on new-born babies in cases of exstrophy of the bladder. Babies are accustomed to anoxia and stand operation well. There is therefore no reason why an intersex baby should not be explored immediately at birth, and there is every reason why it should be because of the havoc which such an individual brings to a family. If, upon exploration, the baby is found to have ovaries, the clitoris should be amputated at once and the mother told that she has a girl baby. If testicles are found the mother should be told that she has a boy who has hypospadias that can be cured when he is 4 years old. There is no place in the world for an intersex individual. The sensational accounts appearing in the newspapers of today of girls being changed into boys and boys into girls are not tributes to modern medical science but a terrible indictment of the medical profession who did not make this determination when it should have been made: on the day of birth of the individual.

It can be seen from the case which I have presented the tremendous influence of psychic sex. This patient was unquestionably predominantly a gonadal female and, I believe, a genetic female, but because the individual had been raised as a boy, everything else to the contrary, he insisted upon living the life of a boy and being surgically constructed into a male. Psychic sex is something not to wait for but to be developed; all the more important is it that the gonadal sex should be determined at the earliest possible date. I am not, however, advocating the change of psychic sex of an individual on gonadal findings alone later in life.

The case which I have reported brings out an important surgical procedure which I have previously described.[4] In 1949 Howard[5] published an article in which he pointed out the high degree of feminism in cases of hypospadias where the urethra opened in the perineum, and that these cases showed a vagina, uterus and tubes. It occurred to me, therefore, that since I had cured many cases of perineal hypospadias in which a vagina was present but unknown to me, that

[3] Cecil, A. B.: Discussion. Trans. West. Sec. A.U.A., p. 125, 1950.
[4] Cecil, A. B.: J. Urol., **62**: 709–712, 1949.
[5] Howard, F. S.: Surg., Gynec. & Obst., **86**: 307, 1948.

in the case which I have presented it would not be necessary to remove the vagina as had previously been advocated in such cases. I therefore constructed the terminal urethra as I have described, and anastomosed the urogenital sinus with the urethra. The vagina has given no evidence of its presence. I am therefore convinced that it is surgically proper not to remove the vagina in intersex individuals where male construction is to be carried out.

ADDENDUM

Since presenting this paper, Moore, Graham and Barr have described a method for the detection of chromosomal sex by a skin biopsy (Surg., Gynec. & Obst., **96**: 641, 1953).

1136 W. Sixth St., Los Angeles 17, Calif.

DISCUSSION

Dr. Samuel A. Vest (Charlottesville, Va.): I note Dr. Cecil said that he didn't believe in any of us taking a hand in making any changes, psychic or sexual, in such hermaphrodites. I have noted a number of these that have changed themselves at older ages.

I remember vividly two cases that Dr. Hugh Young had—two girls—so-called girls—of about 16 and 17, sisters, who were brought to the hospital because the other women in the neighborhood noticed that they were acting up a little bit when they would all go in the toilet together. That created some curiosity, even on the part of the parents. They brought them in, and although they had been raised as girls, their psychic sex changed into the male at that late age, and the perfectly obvious thing to do was to change them into boys at that time.

Dr. A. I. Dodson (Richmond, Va.): As Dr. Hooper has pointed out, we feel that we are quite amiss in not suspecting a malignancy in our patient.

He was treated quite a while by his local physician, and had three visits in my office before I sent him to the hospital. This was partly a result of his reluctance to go to the hospital. He feared any operation upon his testes, because he was afraid that he would lose them.

I am not at all in favor of biopsies in cases of suspected malignancy of the testes, but this man had insisted that his testes must be preserved. The biopsies in this case consisted of an amputation of the entire suspicious area, right across the testes, leaving only a third of the testes when the specimens were sent to the laboratory.

When the report of frozen sections was received, he was under the anesthetic. He had been so insistent upon preserving his testes that I called his wife and talked to her. She was very unhappy about it, but in view of the fact that his life was in jeopardy, agreed to have them removed.

Unfortunately, I lost sight of this man after he left the hospital. We had his telephone number on the record, so we called him when this paper was being prepared. He came by the office. He insists that he feels fine and that his sex function has not been impaired. We feel that it has been long enough to hope that we have cured him.

I would like to say one word about Dr. Patton's paper. For some time we have been interested in polycystic disease, and feel that in a limited and selected few, decompression of the cyst does prolong the patient's life and certainly makes him more comfortable.

I have one patient living, following this operation in 1941.

All of the patients that I have operated upon have had immediate depression of the renal function, as indicated by estimation of dye elimination, but all of those that I have had an opportunity to check have eventually had improvement in renal function.

The patient who was operated upon in 1941 has almost normal renal function now. Interestingly enough, she was admitted to the hospital last year with a mass

in the region of the right kidney, and although the pyelograms did not indicate any involvement of the kidney, we made an incision over the mass, with the idea that it was an isolated cyst. We found that the patient had an enormous cyst of the liver. The abdomen was opened, and the liver—as much as could be seen—was riddled with large cysts. Many of these, of course, were ruptured, or excised, and at the present time the patient is entirely comfortable.

DR. ARTHUR B. CECIL (Los Angeles, Calif.): May I reply to Dr. Vest? It seems to me that the case reported by Dr. Vest was a psychic male as shown by his conduct. Dr. Young only corrected the anatomical deformity.

RENAL FUNCTION STUDIES IN POLYCYSTIC DISEASE OF THE KIDNEY: A PRELIMINARY REPORT

JOHN F. PATTON (Col. MC) AND NEAL S. BRICKER (1st Lt., MC)

From the Urology Section, Surgical Service; and the Research and Development Branch of the Fitzsimons Army Hospital, Denver, Colo.

Little information is available regarding discrete renal function studies in polycystic kidney disease. It is the purpose of this communication to report certain preliminary results obtained in the study of renal functions and electrolyte excretion in patients with this disease, evaluated prior to and following surgical decompression of the kidneys. The data include pre- and postoperative measurements of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), maximum tubular secretion of p-aminohippurate (Tm_{PAH}), and renal excretion of sodium, chloride and potassium.

CASE MATERIAL

The present studies were performed on two adult male patients, both on active military duty at the time of diagnosis. The diagnosis of polycystic renal disease was based upon standard criteria, including dull persistent flank pain, bilateral palpable abdominal masses, and characteristic x-ray patterns following intravenous and retrograde urography. Case 1 (aged 40) was untreated prior to entrance into the hospital (fig. 1, *A*). Case 2 (aged 30) had been exposed to a surgical procedure for decompression of one kidney four months before the time of the present studies (fig. 1, *B*). Control data on case 1, therefore, precede surgical decompression of either kidney; whereas control data on case 2 precede decompression of the unoperated kidney. Postoperative studies were performed 5 weeks following surgery in case 1 and 6 weeks following surgery in case 2.

Surgical exposure of the kidney was performed through the usual lumbar approach. The operated kidneys were fully exposed and decompression was effected as completely as possible by excision of the larger cysts, destruction of the smaller cysts by multiple linear incisions through the cortex and aspiration of the deep cysts. An attempt was made to preserve normal parenchyma. Photographs of the kidneys before and after decompression are reproduced in figures 2 and 3.

METHODS

The pre- and postoperative studies were performed in the morning with the patients in the fasting state. One liter of water was administered 60–90 minutes before studies were begun. Additional water in 200 cc amounts was offered twice during the course of each series of clearance measurements in order to maintain urine flows in excess of 2 cc per minute.

Venous blood samples were drawn through an inlying 17-gauge thin-walled needle into heparinized syringes and discharged into heparinized tubes. A total of 0.1 cc of heparin was used per 10 cc of blood. Following each sampling of blood, 0.3 cc of a dilute (1:10) solution of heparin was instilled into the needle and the needle closed with a Luer-plug. Because no difficulty with clotting was experi-

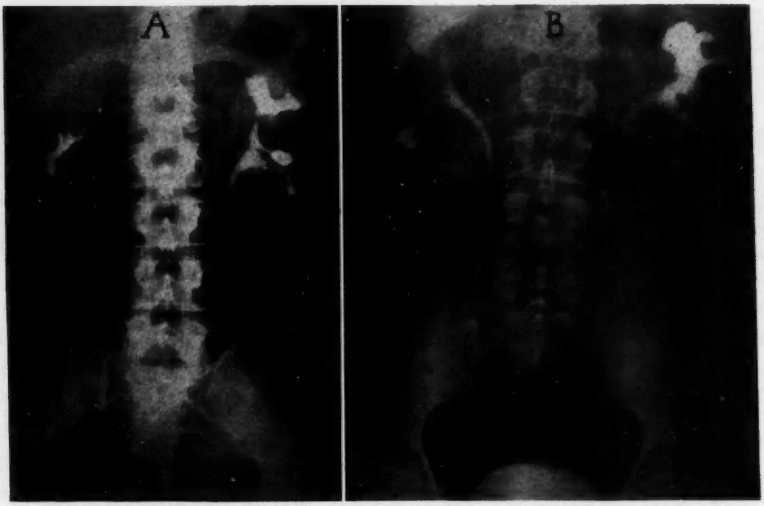


FIG. 1. *A*, retrograde pyelograms in case 1 prior to surgery. *B*, retrograde pyelograms in case 2 prior to surgery.

enced in runs up to five hours in duration, this method was preferred to the use of polyethylene catheters which frequently necessitated venous exposures. To prevent dilution from the heparin in the needle, a 2 cc blood sample was aspirated (in a separate syringe), and discarded prior to each sampling.

The bladder was catheterized with a multi-eyed rubber catheter. Two minutes before the completion of each urine collection period, bladder-washing was initiated. Two successive 10 cc aliquots of sterile distilled water were used, followed by two or more instillations of air. The latter was accompanied by suprapubic pressure. The total washout period was designed to last 2 minutes.

A timed urine sample and a blood sample were collected prior to administration of inulin and PAH primes for determination of inulin and PAH blanks. Prime injections were calculated to yield a plasma inulin concentration of approximately 30 mg. per cent and a PAH concentration of 2–3 mg. per cent.*

Sustaining infusions were administered in a normal saline vehicle through rubber tubing into the "inflow arm" using a constant infusion pump.† Sustaining solution A (inulin-clearance: C_{in}; and PAH clearance: C_{PAH}) was delivered at 1.5 cc per minute. Sustaining solution B (C_{in} and Tm_{PAH}) was delivered at 3.0 cc per minute. Rates of flow were calibrated at 15–30 minute intervals and were found to vary less than one per cent from the predicted rate.

Following administration of the priming injections and the start of sustaining solution A, a period of 30–40 minutes was allowed for equilibration of plasma

* Inulin was obtained as 10 per cent solution from William R. Warner; PAH as sodium para-amino-hippurate in 20 per cent solution from Sharpe and Dohme; Heparin as heparin sodium injection from Lederle Laboratories.

† Bowman Infusion Pump Model 2: Process Instruments Co., 60 Greenpoint Ave., Brooklyn, 22, N. Y.

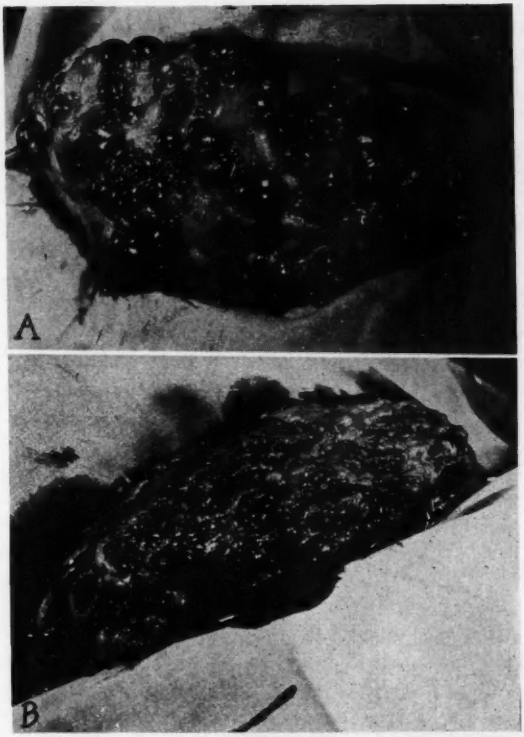


FIG. 2. Photographs of exposed kidney in case 1, before and after surgical decompression.

concentrations of inulin and PAH. Three to four 15–20 minute clearance periods were employed for determination of C_{in} and C_{PAH}. Priming for Tm_{PAH} measurements was accomplished by the administration of 60–70 cc of PAH through a three-way stopcock in the infusion tube at the rate of 10 cc per minute. A second period of equilibration was allowed and three 15–20 minute periods were employed for measurement in C_{in} and Tm_{PAH}. Blood was collected at the midpoint of each period and centrifuged immediately. Plasma was separated for analysis of inulin, PAH, Na, K, and Cl. Inulin was determined according to a modification of the method of Roe et al.[1] PAH was determined according to the method of Smith et al.[2] Chloride was determined according to the method of Van Slyke and Hiller.[3] Na and K were determined on a Baird internally compensated flame photometer.

[1] Roe, J. H., Epstein, J. H. and Goldstein, N. P.: A photometric method for the determination of inulin in plasma and urine. J. Biol. Chem., **178:** 839, 1949.

[2] Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M.: The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest., **24:** 388, 1945.

[3] Van Slyke, D. D. and Hiller, A.: Application of Sendroy's iodometric chloride titration to protein-containing fluids. J. Biol. Chem., **167:** 107, 1947.

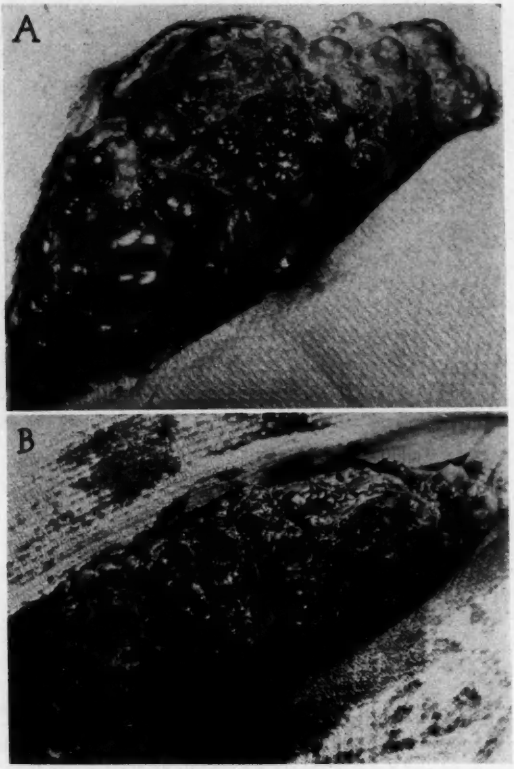


FIG. 3. Photographs of exposed kidney in case 2, before and after surgical decompression.

Plasma and urine inulin recoveries were run with each set of unknowns as a check on the degree of analytical accuracy. Recoveries averaged 100 per cent with extremes of 94 to 106 per cent. All inulin used was drawn from a single lot, which was found to be fructose free by yeasting aliquots prior to analysis by the resorcinol method.

Clearances were calculated by standard methods[4] without correction for delay time.

RESULTS

Average values for renal clearances are recorded in table 1.

Glomerular filtration rate. Low values for inulin clearance were obtained in both patients in control (i.e. preoperative) studies. The deviation from normal was more marked in the patient who had undergone previous decompression of one kidney (case 2), but, in this patient, the disease itself was more advanced.

[4] Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease. New York: The Commonwealth Fund, 1944.

TABLE 1. *Renal function in polycystic disease of the kidneys: Studies before and after surgical decompression of cysts*

	CASE 1			CASE 11		
	Preoperative	Post operative	% Change post-op.	Preoperative	Post operative	% Change post-op.
C_{in} (prior to PAH loading)..	85.5	79.7	−6.8	66.8	45.8	−31.4
C_{PAH}	383.	366.	−4.4	288.	196.	−29.2
F.F. × 100.....	22.5	21.8		23.2	23.4	
TM_{PAH}.....	77.4	60.3	−22.1	42.7	39.2	−8.2

Values represent the average of three or more successive determinations.

Definition of symbols:

C_{in} = inulin clearance (cc/min.)

C_{PAH} = PAH clearance (cc/min.)

F.F. = filtration fraction $\left(\frac{C_{in}}{C_{PAH}}\right)$

TM_{PAH} = maximal tubular excretion PAH (mg/min.)

C_{in} values used in calculating F.F. were obtained prior to PAH loading.

All values are corrected to 1.73 sq.m. body surface area.

Following surgical decompression a further decrease in filtration rate was noted in both patients. In case 1 the decrease in C_{in} was slight; in case 2 the decrease was more marked, amounting to 31.4 per cent of the preoperative value.

Effective renal plasma flow. Clearance of PAH tended to parallel C_{in}. Both patients had control values considerably below normal. Following surgery C_{PAH} declined slightly in case 1, and to a greater degree in case 2.

Filtration fraction. The ratio of C_{in}:C_{PAH} was within the normal range[5] in both cases preoperatively. Following surgery, filtration fractions remained essentially constant illustrating the parallel nature of the changes in C_{in} and C_{PAH}.

Maximal tubular secretion of PAH: The average preoperative value for Tm_{PAH} was normal in case 1 and depressed in case 2. Following surgery, Tm_{PAH} declined in both cases. The greater decrease occurred in case 1, whereas C_{in} and C_{PAH} declined to a greater degree in case 2. In view of the known lability of Tm_{PAH} the magnitude of Tm changes cannot be interpreted at this time.

Excretion of electrolytes. Data on plasma concentrations and minute rates of excretion of Na, K, and Cl, together with computations of filtered load of Na and K are recorded in table 2. The figures for filtered load are uncorrected for plasma water content and the Donnan effect. Computations of the per cent of filtered Na and K excreted ($C_{Na,K}$:C_{in}) are included to illustrate the change in electrolyte excretion following PAH loading in the postoperative as compared to the preoperative state. The control values for this ratio are not intended to indicate the efficiency of tubular reabsorption of electrolytes.

Sodium. Plasma sodium values were within the normal range in all instances. Following PAH loading, which imposes the necessity of excreting large amounts of anion, the excretion rate of Na increased abruptly in all experiments. In both

[5] Smith, H. W.: The Kidney; Structure and Function in Health and Disease. New York: Oxford University Press, 1951.

TABLE 2. *Renal excretion of electrolytes in polycystic disease of the kidneys before and after PAH loading (pre- and postoperative studies).*

PT.	STATUS	CONDITION OF EXPERIMENT	Cin cc/min.	Na				Cl		K			
				P_{Na} mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{C_{Na}}{C_{in}} \times 100$	P_{Cl} mEq/cc	E.R. mEq/min.	P_K mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{C_K}{C_{in}} \times 100$
1	Pre-op.	Control (2)	80.9	.146	11.8	.368	3.12	.111	.322	.0045	.366	.099	27.2
		PAH loading (2)	81.7	.147	12	.873	7.3	.109	.317	.0043	.352	.121	34.6
	Post-op.	Control (3)	79.7	.142	11.3	.249	2.3	.110	.209	.0038	.303	.075	24.63
		PAH loading (3)	67.8	.144	9.7	.60	6.2	.109	.161	.004	.271	.877	32.4
11	Pre-op.	Control (1)	84.2	.142	11.9	.498	4.2	.110	.426	.0045	.377	.094	24.9
		PAH loading (1)	97.4	.144	14.1	.767	5.5	.106	.331	.0038	.372	.079	21.2
	Post-op.	Control (4)	58.5	.144	8.35	.329	3.9	.109	.332	.0046	.269	.084	31
		PAH loading (3)	54.9	.147	8.08	.738	9.2	.108	.342	.0042	.232	.095	41.1

Number of determinations from which values are derived is indicated in parentheses.
Definition of symbols:
P_{NA}, P_{CL}, P_K = Plasma concentration of designated electrolyte;
F.L. = Filtered load (plasma concentration × C_{in}); E.R. = Excretion rate (urine concentration × minute urine flow); $C_{ELECTROLYT}/C_{in} \times 100$ = per cent filtered load excreted; other definitions are included in Table 1.
Values for C_{in} are uncorrected for surface area.

cases, the ratio $\frac{C_{Na}:C_{in}(\text{Control})}{C_{Na}:C_{in}(\text{PAH load})}$ decreased following surgery. Although this is suggestive of a decreased ability of the tubules to retain Na postoperatively under the conditions of the experiment, alternate explanations are possible.

Potassium. Plasma K levels were consistently within the normal range. The ratio of $C_K:C_{in}$ was above that found in the presence of a normal filtration rate,[6] however the comments made above regarding this ratio appear to pertain to K as well as Na. The ratio $\frac{C_K:C_{in}(\text{control})}{C_K:C_{in}(\text{PAH load})}$ decreased following surgery in both cases.

Chloride. Plasma chloride values were within the normal range in both cases in all studies. The effect of PAH loading upon the excretion rate of chloride was inconclusive.

DISCUSSION

There has been an increased interest in the surgical treatment of polycystic disease of the kidneys during the past decade as evidenced by the writings of Goldstein,[7] Cahill and Fish,[8] Dodson,[9] Rathbun,[10] Newman,[11] Howard[12] and

[6] Earle, D. P., Farber, S. J., Alexander, J. D. and Pellegrino, E. D.: Renal function and electrolyte metabolism in acute glomerulonephritis. J. Clin. Invest., **30:** 421, 1951.
[7] Goldstein, A. E.: Polycystic renal disease with particular reference to author's surgical procedure. J. Urol., **66:** 163, 1951.
[8] Cahill, G. F. and Fish, G. W.: Surgical aspects of polycystic disease. Trans. Am. Assoc. G.-U. Surg., **34:** 81, 1941.
[9] Dodson, A. I.: Surgical treatment of polycystic disease of the kidney. J. Urol., **57:** 209, 1947.
[10] Rathbun, N. P.: Polycystic disease. Trans. Am. Assoc. G.-U. Surg., **35:** 131, 1942.
[11] Newman, H. R.: Congenital polycystic diseases. Am. J. Surg., **80:** 410, 1950.
[12] Howard, T. L.: Personal communication.

others. There is general agreement among these authors that in selected cases renal function is improved and life is prolonged by surgical intervention. The mechanism by which this occurs is not clearly defined but the accepted explanation is that decompression of the kidney by rupture of the cysts results in release of untoward pressure on the remaining functioning nephrons.

This present study cannot be considered as an assessment of the value of surgical treatment, since the follow-up period is insufficient. Temporary impairment of renal function is not infrequently observed following a variety of surgical procedures on the kidney; and when impairment already exists recovery from the surgical insult may be protracted. Prolonged studies will be necessary to determine ultimate results.

The possibility exists that the cystic nephrons may serve as functioning units. In postmortem studies performed on two cases of polycystic disease, Lambert[13] was able to demonstrate inulin in the cyst fluid 15 and 96 hours after ante-mortem intraperitoneal inulin injection. In studies performed in this laboratory[14] inulin has been administered intravenously to polycystic patients at the time of surgery and fluid has been aspirated directly from numerous cysts. It has been found that inulin may appear in the cyst fluid within a matter of minutes in appreciable concentrations. If the inulin entering the cysts can be attributed solely to glomerular filtration, the connection of the cysts to functional glomeruli appears likely.* Further studies performed by Lambert[13] and by the present authors[14] have revealed a wide range of creatinine concentrations in fluid taken from different cysts in the same kidneys. The presence of a gradient of creatinine concentrations suggests that the cysts may be intimately associated with functioning tubules, and the corollary exists that the more concentrated the creatinine the more distal the cyst lies along the course of the nephron. Finally, postmortem reconstruction of cystic nephrons of polycystic kidneys by Lambert[13] and Norris and Herman[15] has revealed a glomerulo-tubular continuity of cystic nephrons.

This accumulation of data gives credence to the concept that the cysts are attached dynamically to functioning nephrons, and if this is true, the process of decompression of the kidneys by destruction of cysts may involve loss of multiple functioning units. In light of this, it may be postulated that if the procedure is to improve function it must relieve compression of normal renal parenchyma sufficiently to compensate for this loss. Further evaluation of these concepts is indicated.

SUMMARY

Renal function and electrolyte excretion have been studied in 2 patients with polycystic renal disease before and after surgical decompression. Function was depressed prior to surgery in both patients and further depression was noted 5 and 6 weeks following surgery.

* Studies are in progress to evaluate the possibility that some inulin may enter the cyst fluid by diffusion across the cyst wall.

[13] Lambert, P. P.: Polycystic disease of the kidney. Arch. Path., **44:** 34, 1947.

[14] Bricker, N. S., and Patton, J. F.: Studies of the dynamics and chemical anatomy of cyst fluid in cystic disease of the kidneys (abstract). Clin. Res. Proc. **2:** 22, 1954.

[15] Norris, R. F. and Herman, L.: Pathogenesis of polycystic kidneys: reconstruction of cystic elements in 4 cases. J. Urol., **46:** 147, 1941.

Plasma concentrations of Na, K, and Cl were within normal limits in all experiments. The excretion of Na and K relative to filtration rate was increased by PAH loading to a greater degree in the postoperative state than in the preoperative state.

The possibility that cystic nephrons contribute to renal function was discussed.

The authors give credit to Dr. C. A. Moyer who provided the stimulus for this study, and also acknowledge the invaluable assistance of Claude H. Schmidt, 1st Lt., M.S.C.; Ronald T. Caldwell, B.S., Pfc.; Doris C. Gomez, B.S.; and Melicent E. Hane, B.S.

RETROPUBIC PROSTATECTOMY: A REVIEW OF 678 PATIENTS

ROBERT LICH, JR.

From the Section on Urology, University of Louisville School of Medicine, Louisville, Ky.

This is a survey of 678 patients having undergone retropubic prostatectomy during the 6-year period from 1947 to 1953. The discussion will neither set forth the method nor extol the merits of this procedure. However, to provide a more comprehensive perspective of the status of retropubic prostatectomy I have included a comparable number of cases from both the domestic and foreign literature.

In this group of 678 retropubic prostatectomies there is included 171 patients operated upon by the resident staff of the Louisville General Hospital. All other patients were private patients upon whom the surgery was performed by the late Dr. Owsley Grant, Dr. Joseph E. Maurer and the author.

This series of retropubic prostatectomies includes a 22 month period during which other types of prostatectomy were seldom done. Actually this program was stimulated by correspondence between Dr. Owsley Grant and Mr. Terence Millin. Dr. Grant was anxious to substantiate our contention of perineal superiority and at the same time demonstrate the limitations of Mr. Millin's procedure. Following this initial series of retropubic prostatectomies we resumed our previous practice of employing open prostatectomy only in medium to large prostatic adenoma (in excess of an estimated 60 gm.) (fig. 1).

The following topics have been chosen as the basis for our evaluation of retropubic prostatectomy:

1) Postoperative hospital stay (days)

2) Complications: a. Osteitis pubis; b. secondary hemorrhage; c. mortality. There are of course many additional subjects that might be discussed: Vesical neck contractures, necessity of transfusion due to blood loss at the time of surgery, length of catheter period, etc. all are of interest, but the significance of these complications would certainly be reflected indirectly by the topics chosen for comparison. May I say at this point that we have experienced three vesical neck contractures in our series and all in the first 50 patients when we did not understand when and how much of the vesical neck need be resected. In our private patient series the number of transfusions has been less than 12 per cent while in the general hospital series it approaches 90 per cent. This variation is due to our conservative attitude; whereas, in the general hospital the condition of the patients is less good and the popularity of transfusion is evident on all services.

The domestic and foreign series of retropublic prostatectomies for comparison were chosen at random from the literature based only on obtaining a total group size comparable to our series.

In reviewing tables 1, 2 and 3 there is apparent a remarkable similarity (fig. 2). The increased period of postoperative hospitalization in the foreign series is probably not significant since the time of the retention catheter and postoperative complications did not account for a prolonged hospital stay. It would seem that some other factor must be responsible that was not presented.

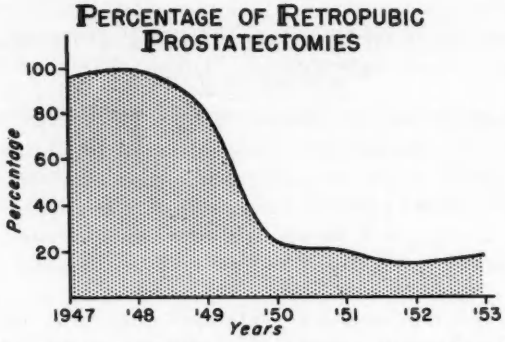


FIG. 1. Percentage of retropubic prostatectomies done annually 1947–1953

TABLE 1. *Domestic series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Hand and Sullivan	100	13.5	0.0	0.0	0.0
Bacon	102	12.6	0.9	0.9	6.8
Toulson, Mays and Hawkins	105	14.3	0.0	0.0	4.7
Moore	116	10.6	11.2	0.0	1.7
Slotkin	119	11.6	0.0		1.6
Scheinman	121	11.4	0.0	0.0	0.0
Total	663	Average...12.3	2.0	0.9	2.4

TABLE 2. *Foreign series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS DAYS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Ostenfeld	114	23	4.3	6.1	5.0
Hickey	50		2.0		2.0
Jacobs	500	16	0.6	0.2	6.0
Total	664	Average...19.5	2.4	3.1	4.3

Osteitis pubis is unquestionably the most disquieting factor in retropubic prostatectomy. It is disturbing because of the variable incidence reported (ranging from 0 to 17 per cent). In discussing this complication with authors who have found it most troublesome, we find no apparent difference in technique and often the author reporting the greatest difficulty seemingly exerts great effort in its prevention. Antibiotics are not a factor for we have done many in which neither antibiotics nor any of the sulfonamides were used. Infections in the space of Retzius are not necessarily significant and we have not found any correlation (fig. 3).

TABLE 3. *Present reported series of retropubic prostatectomies*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Total.....	678	Average...12.1	0.7	1.3	1.6

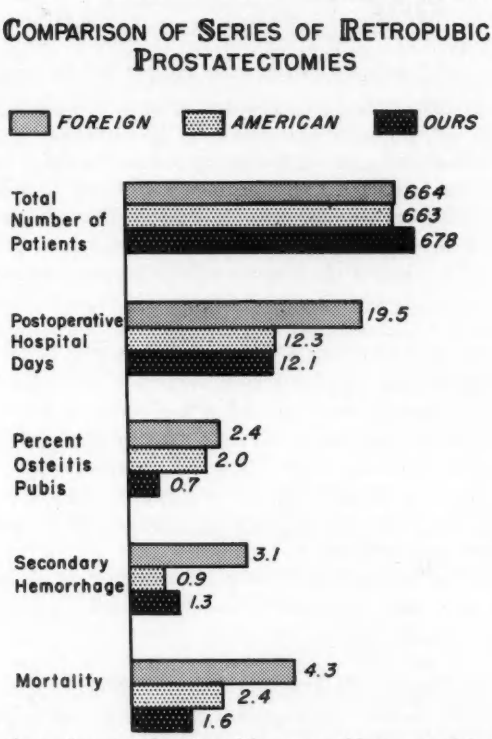


FIG. 2. Comparison of reported series with comparable group of American and foreign authors.

In fact, in only one of our 5 patients with osteitis pubis was there any appreciable visible wound infection. Our incidence of wound infection, of sufficient intensity to warrant additional hospitalization, was found to be 5.3 per cent or a total of 36 wounds. The incidence of osteitis pubis was 0.7 per cent or a total of 5 patients. One of the 5 patients with osteitis pubis occurred in the General Hospital series of 171 patients. Only two patients suffered severe and prolonged symptoms. Millin in reporting 1100 cases of retropubic prostatectomy mentions 9 instances of osteitis pubis; an incidence of 0.8 per cent.

We have used secondary hemorrhage to connote postoperative hemorrhage that has occurred after the initial operative bleeding has subsided. In reviewing

FIG. 3. Relationship between osteitis pubis and retropubic wound infection

the literature it is difficult to judge the definition of secondary hemorrhage as used by some authors. For example, secondary hemorrhage occurring after the catheter has been removed and controlled by re-insertion of a catheter has not been considered in our series to be significant provided that it did not prolong the patient's postoperative course. The criterion used in our series was hemorrhage that necessitated some type of operative intervention. In the group reported it was controlled in all but two of the 9 patients suffering this complication by transurethral fulguration of the bleeding vessel. In two instances the bleeding point could not be localized transurethrally and the operative wound was reopened and the prostatic bed packed which controlled the bleeding immediately. In one instance the bleeding was coming from a large vein in the cut edge of the prostatic capsule anteriorly and in all other patients the bleeding was due to a prostatic artery. Because of these experiences all vessels in the capsular wound edge are securely ligated with a figure of eight suture as are the prostatic arteries. This single variation from Mr. Millin's original technique has put an end to our problem of secondary hemorrhage. We employ fulguration for small oozing points, but never for active arterial bleeding.

In this group of 678 patients there were 11 deaths or an incidence of 1.6 per cent. Except one, all deaths occurred within 14 days following surgery. The one exception was a patient of 73 years who died suddenly 27 days following surgery after he had ridden home, a distance of 58 miles, on his eighth postoperative day. One patient, 56 years of age, died on the fifth day after surgery with an acute coronary thrombosis; another, 78 years of age, had an uncontrollable cardiac decompensation and bronchopneumonia and died in cardiac failure on the thir-

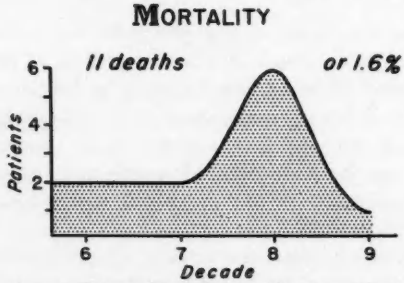


FIG. 4. Comparison of mortality to patient's age

teenth postoperative day. A man of 66 years died of an overwhelming perivesical infection which had presumably been present, though undiagnosed, preoperatively. This patient had tolerated neither urethral nor cystotomy drainage since both had been used in an attempt to avert prostatectomy and in desperation a prostatectomy was executed. He must be considered as an ill chosen subject for prostatectomy. One patient of 72 years died within 8 hours after surgery during which time he did not respond from the anesthetic; the cause of death was not determined. One patient of 78 years entered the operation with reluctance and postoperatively he grew steadily worse and died on the eleventh day after a series of small cerebral accidents. An 87 year old man, in exceptionally good physical condition, died suddenly on the day prior to discharge or his seventh day postoperatively from an apparent pulmonary embolus. The remaining four patients of 59, 69, 71 and 77 years died on the sixth, eleventh, seventh and thirteenth days respectively of an infarct, cardiac failure, bronchopneumonia and uremia.

Considering that these 678 operations were done in five different hospitals with a wide variation in hospital facilities and personnel available the mortality incidence of 1.6 per cent is an acceptable figure.

SUMMARY

A report has been made of 678 patients who have undergone retropubic prostatectomy. This series is discussed briefly and a comparison is made between a comparable domestic and foreign series.

801 Heyburn Bldg., Louisville 2, Ky.

REFERENCES

BACON, S. K.: Retropubic prostatectomy: report 102 cases. J. Urol., **61:** 75–77, 1949.

GRANT, O., LICH, R., JR. AND MAURER, J. E.: Retropubic prostatectomy. Urol. & Cutan. Rev., **52:** 9–12, 1948.

GRANT, O. AND LICH, R., JR.: Rationale and results in retropubic prostatectomy. Ann. Surg., **127:** 1010–1021, 1948.

HAND, J. R. AND SULLIVAN, A. W.: Retropubic prostatectomy: analysis of 100 cases. J.A.M.A., **145:** 1313–1321, 1951.

HICKEY, B. B.: Immediate prostatectomy by Millin's method for acute retention of urine. Brit. J. Urol., **22:** 410–413, 1950.

JACOBS, A.: Retropubic prostatectomy: Review of 500 cases. Lancet, **1:** 1088–1090, 1951.

LICH, R., JR. AND GRANT, O.: Extravesical prostatectomy: a comparison of retropubic and perineal prostatectomy. J. Urol., **61:** 930–942, 1949.

LICH, R., JR., MAURER, J. E. AND BURDON, S.: An extravesical method for the relief of vesical occlusion. Arch. Surg., **59:** 460–465, 1949.

MILLIN, T. Retropubic Urinary Surgery. Baltimore: Williams & Wilkins, 1947.

MILLIN, T., MACALISTER, C. L.O. AND KELLY, P. M.: Retropubic prostatectomy: experiences based on 757 cases. Lancet **1:** 381–385, 1949.

MILLIN, T.: Retropubic prostatectomy. J. Urol., **59:** 267–280, 1948.

MOORE, T. D.: Retropubic prostatectomy: Results and complications. J. Urol., **65:** 865–873, 1951.

OSTENFELD, J.: Retropubic surgery in benign prostatic lesions. Acta Chirurgica, **102:** 447–456, 1952.

SCHEINMAN, L. J.: Experiences with retropubic prostatectomy. Northwest. Med., **51:** 118–119, 1952.

SLOTKIN, G. E.: Retropubic prostatectomy: Survey of the indications and results of 119 cases. N.Y. State J. Med., **52:** 220–220, 1952.

TOULSON, W. H., MAYS, H. B. AND HAWKINS, C. W. Experiences with retropubic prostatectomy. J. Urol., **65:** 874 1952.

PROSTATECTOMY, MORTALITY AND MORBIDITY

S. A. MacDONALD

From the Department of Surgery (Urology), McGill University, Montreal, Canada

It is always interesting to compare one era with another. In the history of surgery the chapters or phases of development are separated by dramatic changes. The most recent of these have been due to the free use of blood transfusion and the concurrent introduction of antibiotic therapy. It is well known that these and other influences have produced a marked change in the morbidity and mortality of prostatic surgery. For the purpose of accurately evaluating these changes and of studying their impact in one hospital the records of 1050 consecutive public ward patients submitted to prostatectomy in the Montreal General Hospital have been reviewed.

It should perhaps be mentioned that the majority of these patients come from the poorer districts of a large industrial and sea-port city. Far advanced disease processes and malnutrition are encountered not uncommonly. Despite these adverse influences it was interesting to find that 90 per cent of the entire group had minimal or no elevation of blood urea levels (table 1). The average age was 68.8 years, which probably is considerably higher than that of private patients admitted to the same hospital.

For the purpose of the study 520 patients operated upon prior to 1944 were selected and compared with a second group of 530 patients operated upon in 1947 and later. The years 1945 and 1946 have been selected as a transition period and excluded from the study, for it was during these 2 years that routine adequate blood replacement and the earlier antibiotics were introduced.

The first group of 520 patients were all operated upon in what might be termed the sulfonamide era, between the years 1937 and 1944. All of these patients were treated by the classical suprapubic, two-stage method of prostatectomy. The annual average mortality was 7.6 per cent. This figure compares very favorably with others published for the two-stage operation at that time. The annual mortality rate varied from 12.4 to 3.0 per cent. This extreme variation from year to year of more than 4 to 1 shows the fallacy of basing any statistical study on the results of a single year's work or upon too small a series of patients.

The cases in the second group, consisting of 530 patients, were operated upon in the years 1947 to 1952. During that period the average annual mortality rate fell sharply to 2.0 per cent (fig. 1). In 1947 and again in 1949 no operative death occurred. During that period 5 additional patients had a second stage or two-stage operation without a death. These patients are not included in the analysis. Five more patients who had cystostomy only likewise are not included.

In these two groups of patients operated upon in the same hospital in separate though closely related periods, there is a difference in mortality rate of 400 per cent. The circumstances underlying this change become obvious when the causes of death are analyzed in table 2. In the earlier group, pyelonephritis was the chief killer, accounting for 25 per cent of the combined deaths after the first and second

TABLE 1. *Blood urea levels, 356 consecutive patients*

MG. %	NO. OF PATIENTS	% OF TOTAL
20–30	323	90.7
31–40	9	2.2
41–50	10	2.7
50–90	10	2.7
90+	4	1.1

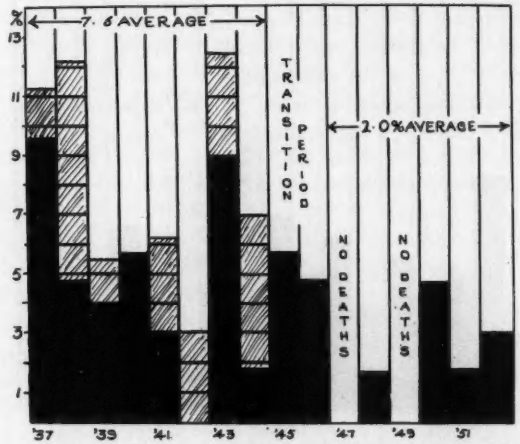


FIG. 1. Annual operative mortality in public ward patients, Montreal General Hospital. Black areas in years 1937–1944 represent second stage deaths; gray areas, first-stage deaths. Black areas from 1945–1952 represent total operative deaths.

TABLE 2. *Causes of operative death*

	1937–1944 8 years	1947–1952 6 years
No. of patients	520	535
Pyelonephritis	10	0
Hemorrhage and shock	9	0
Cardiovascular accidents	9	4
Pulmonary embolism	7	1
Other causes	5	6
Total	40	11

stage operations. In the second group not a single fatality can be attributed to urinary tract sepsis. A similar dramatic change has occurred in the elimination of deaths due to hemorrhage and shock. In the first group, 9 of a total of 40 fatalities were attributed to these latter two causes. In the second group they were not responsible for a single death. Therefore it is apparent that a remarkable change has occurred in the virtual elimination of the two former chief causes of death. Between them they accounted for 50 per cent of all the earlier fatalities.

TABLE 3. *Operative mortality*

TYPE OF OPERATION	NO.	MORTALITY RATE
Transurethral	310	2.5%
One-stage S. P.	196	2.2%
Retropubic	12	0.0%
Perineal	12	0.0%

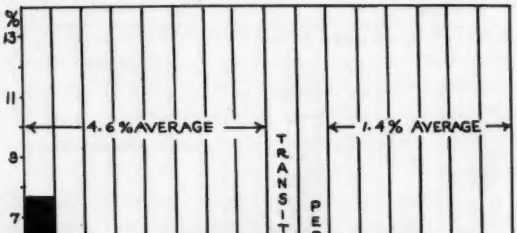


FIG. 2. Annual preoperative mortality in public ward patients, Montreal General Hospital.

TABLE 4. *Causes of preoperative death*

	1937–1944 8 years	1947–1952 6 years
No. of patients	544	539
Pyelonephritis	9	1
Cardiovascular	8	6
Pneumonia	3	0
Pul. embolism	2	0
Uremia	0	2
Other causes	2	0
	24	9

Another important change has been the diminution in the incidence of pulmonary embolism. In the first group of patients 7 fatal emboli occurred; in the second group only one. This further improvement has eliminated an additional 15 per cent of the former deaths. The one remaining significant cause of mortality has been disease of the cardiovascular system, but even its incidence has been reduced by half. It is not likely that the danger of cerebral hemorrhage or thrombosis or coronary infarction can be removed entirely in this older group of patients.

All four, standard, prostatic operations were utilized in the treatment of the more recent group of 530 patients. Most of them, 506 in all, were operated upon by either the transurethral or the one-stage, suprapubic, transvesical procedure. This latter group affords an excellent opportunity for comparing the results of these two operations on the same urological service (table 3). The mortality rate for the two procedures was virtually the same, 2.5 per cent for the one-stage in 196 patients, and 2.2 per cent for the per-urethral in 310 patients. This similarity in mortality rates was somewhat surprising, because an impression had been formed from watching the two groups of patients on the same wards that the mortality in the suprapubic group would be considerably higher. Certainly the suprapubic procedure seems to be a more disturbing operation for the patient, and this fact is borne out by the incidence of immediate postoperative complications, which has been 18 per cent in the one group and 8.3 per cent in the other.

All these changes in operative results are interesting and significant, but the greatest of all seems to be taking place in the reduction of preoperative mortality. In the years 1937 to 1944 there were 24 preoperative deaths with a mortality rate of 4.4 per cent. This is in sharp contrast with the 9 deaths and mortality rate of 1.4 per cent in the period from 1947 to 1952. It would seem that the preoperative fatality rate is still falling for in the past 3 years there has been but a single death, a rate of 0.3 per cent for this three year period. See figure 2.

In the preoperative phase of treatment pyelonephritis again was found to be the commonest cause of death (table 4). It accounted for 9 of the 24 preoperative fatalities in the first group of patients, but was responsible for only 1 in the second group. The incidence of preoperative deaths due to cardiovascular disease in the two groups has remained virtually the same. This may indicate that there has not been a very great change in the general level of health. Deaths from all other preoperative causes have diminished.

The most striking information that has emerged from this study is the startling decrease in deaths due to urinary tract sepsis. It is not likely that this change can be attributed solely to the introduction of antibiotics. Many factors such as less preoperative urethral instrumentation, and greater attention to asepsis have undoubtedly played their part. The change-over from two-stage suprapubic prostatectomy may have had some effect on the mortality rate but under modern conditions the two-stage operation could be performed perhaps with equally good results.

In summary it can be said that the former chief causes of preoperative and operative fatality in prostatic patients virtually have been removed. Further improvement in mortality rates will depend probably on greater attention to the minutiae of treatment and in particular to extreme precautions against cardiovascular accidents.

1414 Drummond St., Montreal, Canada

AVOIDING THE POOR RESULTS IN TRANSURETHRAL PROSTATECTOMY

HENRY M. WEYRAUCH AND MILTON L. ROSENBERG*

From the Department of Surgery, Division of Urology, Stanford University School of Medicine, San Francisco, Calif.

Although transurethral resection has gained wide favor, many urologists find that it yields a higher incidence of poor results than do open types of prostatectomy. Even those who deny a higher incidence of poor results agree that there is a symptom complex following endoscopic prostatic resection that is peculiar to this operation.

In his remarkable contribution, Flocks[1] demonstrated that removal of all edematous and devascularized tissue produces better results. Unfortunately, this expedient does not *assure* a good result. There are those patients who continue to complain of dysuria, nocturia, urgency and frequency of urination, and perineal and rectal pain despite the fact that the prostatic fossa is devoid of obstructive or devitalized tissue, that there is no stricture of the urethra, no urinary infection and no residual urine and that the capacity of the bladder is normal. This is the type of patient who is usually subjected to repeated resections. Yet oftentimes the more resections he has, the worse his symptoms become.

The causes of poor results may be grouped into three categories: 1) deleterious factors inherent in the method, 2) individual variations in operative technique and 3) the influence of the pathologic lesion. By making an intensive study of these factors we have learned some of the causes of poor results and their relative importance. This information has been applied clinically in an attempt to outline measures which will improve the results.

1. DELETERIOUS FACTORS INHERENT IN THE METHOD

One of the outstanding peculiarities of the method is the effect of high frequency currents on tissue. Several years ago we investigated the immediate thermal effects.[2] More recently we have studied the healing process in the prostatic fossa following experimental resections in dogs and by the examination of tissue removed at secondary operation in patients.

Although benign prostatic hypertrophy in the dog is a different pathological process than in man, since there is no surgical capsule defining a peri-urethral adenoma in the dog (fig. 1), the glandular tissue is similar in both and, if one resects into true prostate in the human, after having removed all peri-urethral adenoma, conditions are similar. The glandular tissue just inside the anatomical capsule in both man and dog is supplied by capsular arterial branches (fig. 2).

In the dog, since the os penis renders it impossible to insert a resectoscope through the anterior urethra, in our initial experiments the 16F Nesbit electro-

* Bank of America-Giannini Foundation Research Fellow.

[1] Flocks, R. H.: Local repair following transurethral prostatic resection: Its role in clinical events associated with this operation. J. Urol., **40:** 208–232, 1938.

[2] Weyrauch, H. M., Bassett, J. B., and Berger, M. M.: Practical considerations in use of high frequency currents for transurethral prostatectomy. J. Urol., **61:** 371–383, 1949.

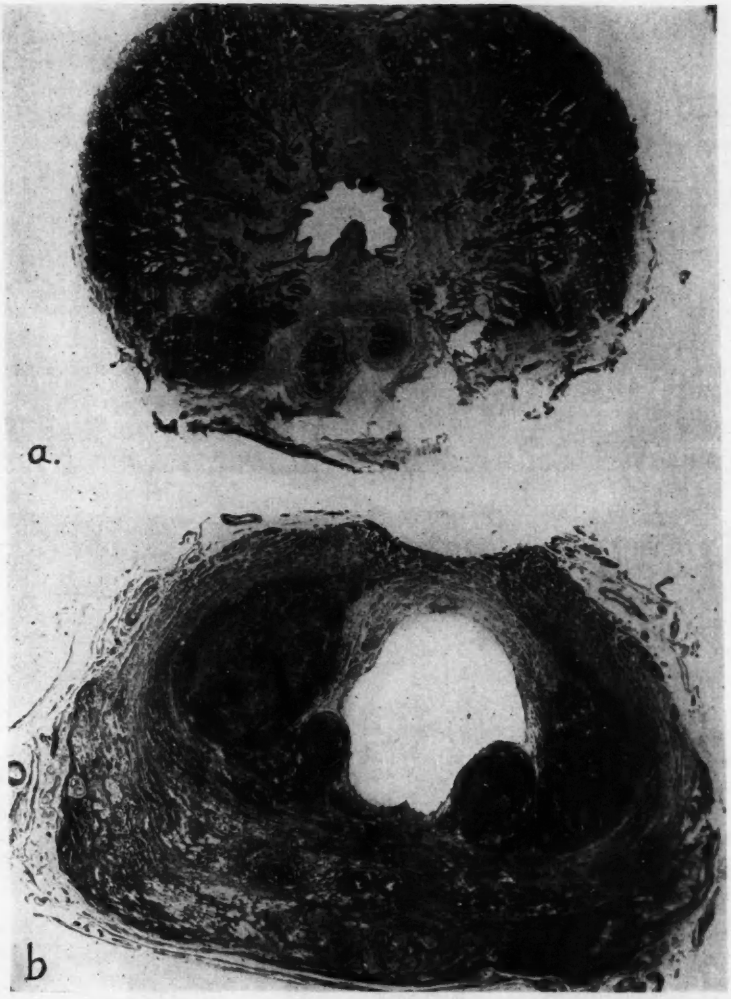


FIG. 1. Cross section of dog prostate, *a*, and human prostate showing benign prostatic hypertrophy, *b*.

tome was introduced through a perineal urethrotomy (fig. 3). In 36 animals the prostate was resected to various levels on one side; the opposite side was left intact as a control (fig. 4).

Postmortem examinations were made at scattered intervals of from two days to nine weeks after operation. The prostate and bladder were removed intact and fixed in formalin after first testing for extravasation. This was done by making manometric readings after ligating the membranous urethra and filling the

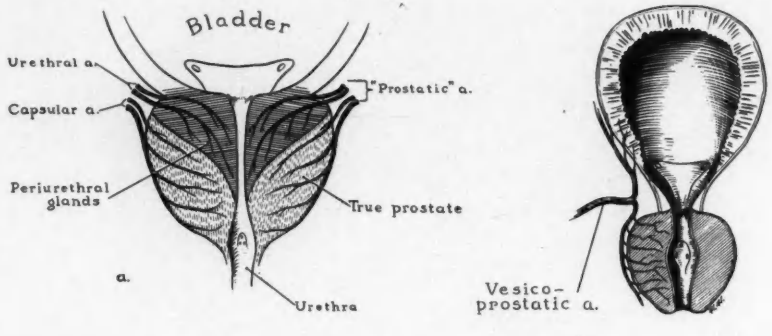


FIG. 2. Arterial blood supply to prostate of human, *a*, and dog, *b*. Capsular vascular supply is similar in both.

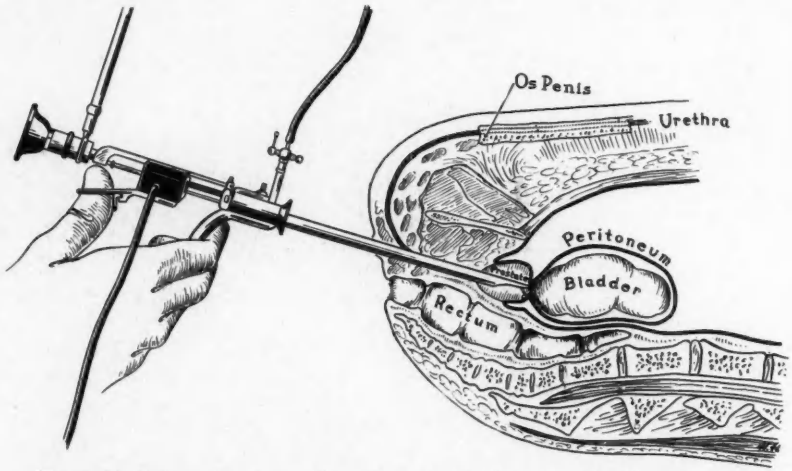


FIG. 3. Technique of endoscopic resection in dog through perineal urethrotomy

FIG. 4. Level of resection in dog; *a*, broad glandular; *b*, narrow glandular; and *c*, aglandular rim. Opposite side left intact as control.

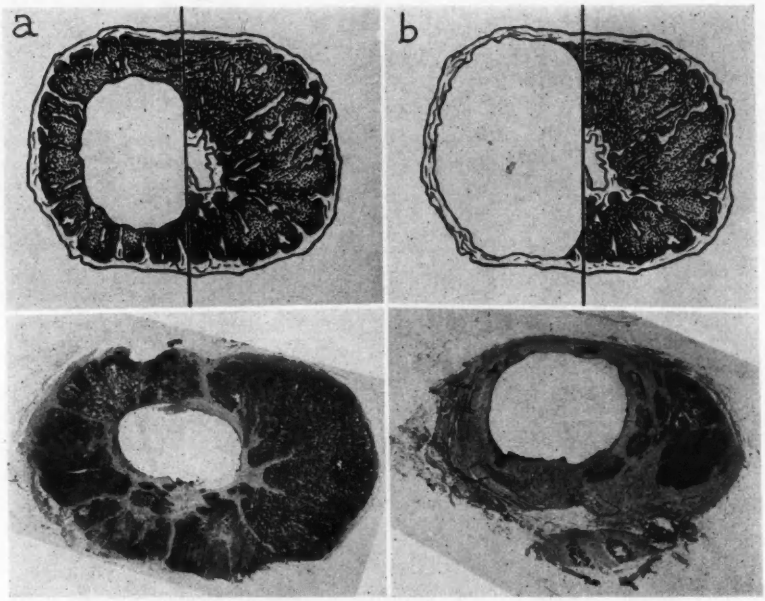


FIG. 5. *a*, Diagram and microscopic section of glandular prostatic rim in dog. *b*, Diagram and microscopic section of aglandular rim in dog.

bladder with water. If the capsule was not perforated at the time of operation, extravasation could not be produced at 100 cm. of water pressure.

Microscopic studies were made of the ureters, kidneys, liver, lung and spleen to ascertain the occurrence of metastatic infection. Cross-sections were made of the prostate to show the healing process. We were particularly interested in comparing the results after leaving a rim of glandular tissue (fig. 5, *a*) with those after denuding the fibrous anatomical capsule (fig. 5, *b*). It is of practical significance to know whether epithelialization progresses more readily on a glandular or fibrous surface following prostatic resection.

In using the 16F resectoscope, considerable technical difficulty was encountered in exposing the fibrous capsule over any large area. Not only was vision extremely limited but the small proportions of the loop proved a handicap. Therefore, in 16 additional experiments, resection was performed through open operation. The prostate was exposed retropubically and an incision made through the anterior commissure into urethra (fig. 6). With the margins of the incision held apart, one side of the prostate was removed with the loop electrode under direct vision (fig. 7). The incision was closed with a continuous suture of chromic catgut, as is employed in retropubic prostatectomy. The closure was water-tight against a sustained pressure of 100 cm. of water.

In these experiments it was found that infection exerted a tremendous influence in preventing healing. In the presence of infection, as shown by widespread

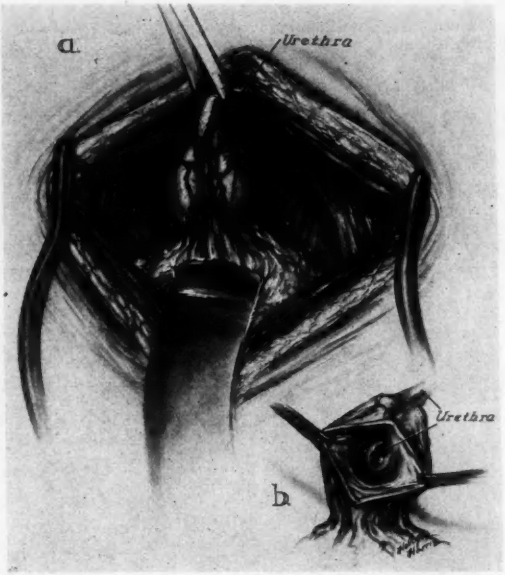


FIG. 6. Retropubic exposure of dog's prostate, *a*, Incision through anterior commissure into urethra, *b*.

infiltration with polymorphonuclear leukocytes, infected ducts and abscess formation, epithelialization was long delayed.

In 16 animals with a glandular rim, killed at one week, healing occurred in six of 11 dogs that were uninfected; in five showing infection, none healed during this period (significant at .08) (fig. 8, *a*). In 4 dogs with a fibrous rim killed at one week, none showed healing. Three of these were uninfected and one was infected. The glandular rim at one week permits healing if there is no infection. In the fibrous rim, one week is insufficient time for healing and the retarding effect of infection, if any, could not be demonstrated. In 40 animals with a glandular rim, followed up to nine weeks, healing occurred in 18 of 23 dogs (78 per cent) that were uninfected and only in five of 17 (29 per cent) showing infection (significant at .01) (fig. 8, *b*).

Since the devitalized surface of the resected area contributes in such large measure to this high incidence of infection, the factor of tissue destruction was further assessed by producing an area of gangene in the prostate of some dogs and by using a cold punch in others. In order to produce gangrene the prostatic artery on one side was ligated at its point of entrance to the capsule after which both lateral lobes were resected with the high frequency loop. In the devitalized resected tissue of three dogs the acini and supporting tissues were atrophied, infection was increased, there were scattered infarcts and healing was delayed. These changes did not occur in tissues with an intact blood supply. In 9 dogs one side of the prostate was excised with the cold punch while the opposite side was

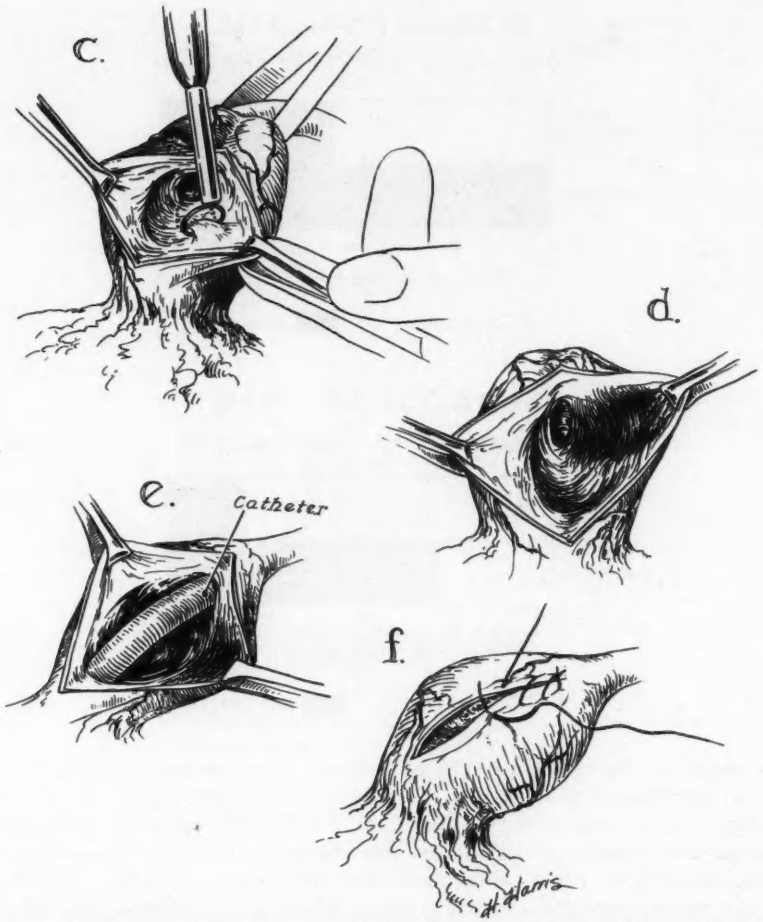


FIG. 7. Electroresection of one side of dog's prostate, *c*. Right lateral lobe has been removed, *d*; urethral catheter inserted, *e*; closure of prostatic capsule *f*.

resected with the high frequency loop. In all 9 dogs the tissue removed by cold resection exhibited less infection, less surface slough, absence of obstructed ducts and more rapid healing than the tissues removed with the high frequency current (significant at less than .01).

As a corollary study to the animal experiments the occurrence of infection in the prostatic fossa was investigated in patients. It was illuminating to discover that a similar high incidence of infection was observed. In 20 patients who had undergone a second transurethral resection for persistent symptoms yet without obvious obstruction, the inflammatory changes in tissue removed at the second operation were compared with the changes observed in tissue obtained at the

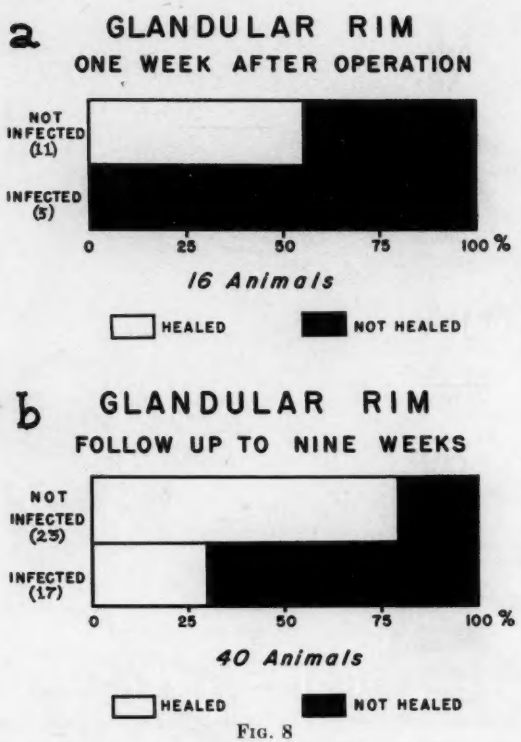


FIG. 8

first operation. In 12 cases the degree of infection was decidedly greater at the second operation than at the first. Seven showed the same degree of infection; in one infection was decreased (fig. 9, *a*). There was a significant correlation between the degree of infection in the prostatic cortex and the severity of symptoms. All patients with severe symptoms showed increased infection. Similarly, those with mild symptoms showed minimal infection. This correlation is demonstrated in figure 9, *b*.

Isolated observations pertinent to the occurrence of infection have been made in several additional clinical cases. In one instance a second resection for benign hypertrophy 19 days after the first showed gross evidence of infection. Pus exuded from every duct opened by the resecting loop, each duct being widely distended with inflammatory exudate. Microscopic examination of the tissue removed from this patient showed occluded, dilated ducts containing pus and surrounded by heavy polymorphonuclear infiltration (fig. 10). Upon performing a cystoscopy a few days after a "complete" transurethral prostatectomy one is frequently appalled to see the amount of tissue which remains in the prostatic fossa. Apparently exudate within occluded prostatic ducts and edema caused by thermal injury are the two factors chiefly responsible for this observation.

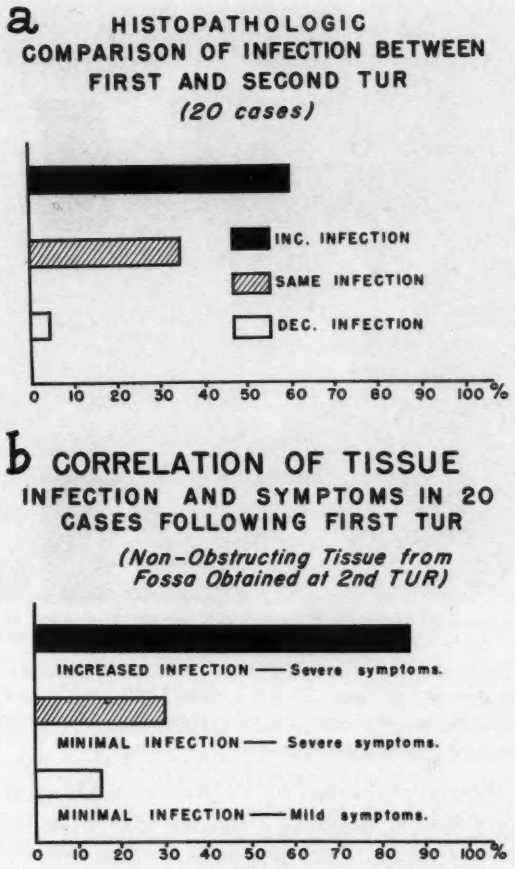

a
HISTOPATHOLOGIC
COMPARISON OF INFECTION BETWEEN
FIRST AND SECOND TUR
(20 cases)
INC. INFECTION
SAME INFECTION
DEC. INFECTION
0 10 20 30 40 50 60 70 80 90 100 %
b
CORRELATION OF TISSUE
INFECTION AND SYMPTOMS IN 20
CASES FOLLOWING FIRST TUR
(Non-Obstructing Tissue from
Fossa Obtained at 2nd TUR)
INCREASED INFECTION — Severe symptoms.
MINIMAL INFECTION — Severe symptoms.
MINIMAL INFECTION — Mild symptoms.
0 10 20 30 40 50 60 70 80 90 100 %

FIG. 9

In another patient who had neither obstruction nor infected urine, at perineal operation for urinary incontinence four years after a first resection, three years after a second resection and one year after a third resection, diffuse periprostatitis was discovered. The patient was completely relieved of perineal and rectal discomfort from which he complained, but only partially relieved of urinary incontinence by a pull-through operation.

This cumulative experimental and clinical evidence indicates that hidden infection in either the prostatic fossa or the periprostatic tissue may account for continued urinary difficulty in patients without obstruction or infected urine.

Another peculiarity of transurethral resection is the destruction of the vesical neck which affords free communication between the bladder and the prostatic fossa. This permits urine, which is usually infected, to remain in constant contact with granulating tissue of the prostatic fossa. In open types of adenomectomy

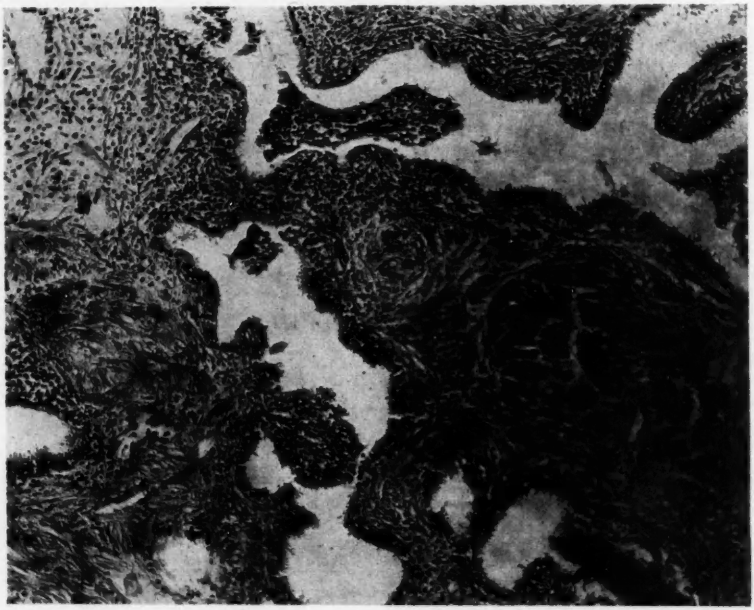


FIG. 10. Tissue removed at second transurethral section. Histologic examination shows occluded, dilated ducts containing pus and surrounded by heavy polymorphonuclear infiltration.

there may be temporary damage to the vesical neck, but it is not extensively destroyed by high frequency currents, and competence of the orifice is frequently restored, as shown by cysto-urethrograms.

2. INDIVIDUAL VARIATIONS IN OPERATIVE TECHNIQUE

Individual variations in operative technique likewise affect the results in transurethral prostatectomy. To begin with, there is considerable confusion about what constitutes a "complete" transurethral prostatectomy. Urologists agree that it is desirable to perform a "complete" prostatectomy. Yet what is a complete prostatectomy for one may represent nothing more than a glorified tunnel to another. The confines of enucleation by any of the conservative open prostatectomies are well defined by the limits of the surgical capsule, supplemented perhaps by a notch taken from the vesical neck. Transurethral resection, on the other hand, can be infinitely varied in what tissue and how much tissue is removed. Some urologists erroneously believe that when they actually bare the fibrous capsule, they are down only to the surgical capsule. Whereas the surgical capsule is easily defined by an enucleating finger, it is not so readily identified through the lens of a resectoscope nor even through the lens of the pathologist's microscope. The experienced resectionist can recognize the fibers of the anatomical capsule or of the vesical neck, but identification of the surgical capsule is difficult to impossible. It would seem more accurate to term this a surgical cleavage plane rather than a surgical capsule.

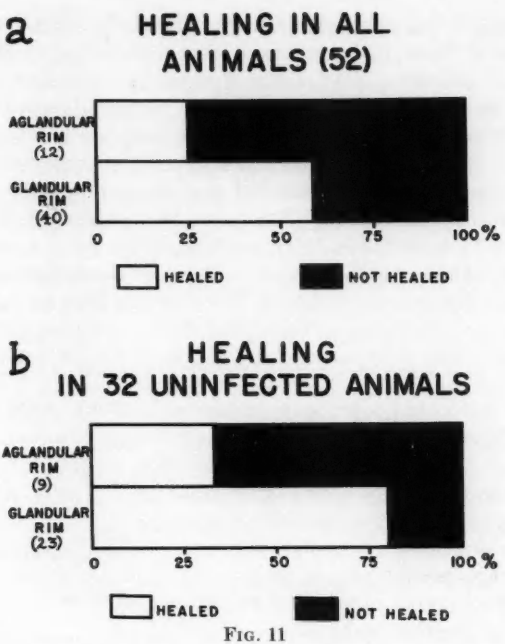


FIG. 11

In the dog, we demonstrated that it is desirable to leave a rim of glandular tissue, substantiating the premise that a well-nourished zone of glandular tissue is more conducive to prompt healing than a barren expanse of fibrous tissue. In the 52 experiments, 12 animals were resected to the fibrous capsule with healing in only three (25 per cent), as compared with healing in 23 of 40 dogs (58 per cent) in the presence of a glandular rim (significant at .10) (fig. 11, *a*).

In 32 uninfected animals only three of nine (33 per cent) showed healing over a fibrous capsule, whereas 18 of 23 dogs (78 per cent) healed over a glandular rim (significant at .05) (fig. 11, *b*).

Selecting the proper time to operate may have an important bearing on the immediate postoperative result. Prostatectomy during the early phase of prostatic obstruction may lead to severe urinary discomfort. With removal of the obstruction the hypertrophied detrusor suddenly becomes too powerful. The patient suffers from increased frequency, nocturia, urgency and stress incontinence—symptoms that may persist for several weeks. This clinical problem seems most frequent following transurethral resection, possibly because resection is more often performed in early obstructions.

3. INFLUENCE OF THE PATHOLOGIC LESION

The nature of the lesion is another factor influencing the postoperative result. For example, patients with a fibrous prostate are notoriously difficult to improve by resection. Pathologically, contractures of the vesical neck, median bar and the small prostate *sans hypertrophie* are almost exclusively composed of fibrous

tissue and, from a technical standpoint, are well suited to resection. There is only a small amount of tissue to be removed. The high frequency loop, used under direct vision, is ideal for precise excision of tissue in which there is no fortuitous cleavage plane for open enucleation. Yet ideal though these circumstances appear, the patient is not cured. Maximal resection temporarily relieves the obstruction, but deeper surrounding fibrous tissue reproduces the original condition. A wide, denuded zone of burned, aglandular, fibrous tissue remains after resection. Healing is delayed by the absence of epithelial-lined acini as well as by the scarring tendencies of fibrous tissue.

Another factor which may account for continued difficulty is the presence of prostatic calculi. Persistent infection is inevitable as long as calculi remain as foreign bodies.

MEASURES TO AVOID POOR RESULTS

On the basis of our studies we have attempted to classify what expedients and measures may be taken to avoid poor results following transurethral prostatectomy:

1) Make the proper choice of prostatectomy.
2) Use the optimal operative technique:
   a. Application of high frequency currents.
   b. For benign prostatic hyperplasia.
   c. For fibrous lesions of the prostate and vesical neck.
3) Avoid damaging the urethra.
4) Consider the condition of the bladder.
5) Prevent infection.
6) Hasten separation of slough.

1) *Make the proper choice of prostatectomy.* A certain percentage of poor results can be avoided by revising our views concerning the choice of prostatectomy. Serious consideration should be given to open prostatectomy or the use of the cold punch in the treatment of those lesions that experience has shown are not favorably affected by resection—notably the fibrous prostate. Likewise, when irritative symptoms recur after one or more transurethral resections it seems unwise to follow the dictum which is creeping into our way of thinking, "Once a resection, always a resection." In many instances, following repeated resections, total prostatectomy apparently affords the only reasonable opportunity for permanent relief.

2) *Use of optimal operative technique.* By complying with certain general principles in performing the transurethral operation, the incidence of poor results may be decreased considerably.

With regard to high frequency currents, coagulating currents are the more destructive and potentially dangerous. They should be of as low intensity as practicable. Point coagulation should be used in preference to coagulation of wide areas. It is important that coagulation be kept to a minimum whenever the resection approaches the fibrous capsule. This prevents thrombosis and delayed infection in the venous sinuses and periprostatic tissues. In using cutting currents, the stroke should be rapid and the loop of small caliber.

When the depth of slough exceeds the remaining thickness of capsule, irrespective of whether late perforation occurs, conditions are more propitious for the development of periprostatitis. Bacteria in the necrotic tissue gain easy access to the periprostatic space. Osteitis pubis which occurs following resection without perforation[3] most likely develops in this manner.

The advocates of the cold punch recommend this instrument in preference to an instrument utilizing high frequency currents, reasoning that conditions are more propitious for healing if one eliminates tissue destruction caused by intense heat. Our experiments in the dog appear to substantiate this premise, showing that there is no damage to surrounding tissue, less infection and more prompt healing with the cold punch.

In transurethral resection of the adenomatous gland the first surgical step is to remove all of the peri-urethral adenoma. Complete removal of the adenoma is necessary to avoid the poor results attributable to remnants of devitalized tissue—persistent infection, recurrent hemorrhage, calcareous deposits, continued obstruction—and to eliminate the possibility of recurrence. In addition to removing the adenoma, the resection should be carried into the area of the true prostate, taking care, however, to stop short of "baring the fibrous capsule." By including an additional zone of tissue surrounding the adenoma there is more certainty of removing spheroids and calculi that may be buried in compressed prostatic tissue. This step likewise reduces the zone of prostatic tissue that frequently provides a source of chronic infection. On the other hand, in leaving a narrow rim of glandular tissue in preference to baring the fibrous capsule, epithelialization is accelerated and the dangers of penetrating venous sinuses and perforating the capsule are avoided.

We have been particularly interested to learn modifications of technique which will improve the results in those conditions in which they are so proverbially bad—the fibrous prostate, median bar and contracture of the vesical neck. Various expedients may be attempted.

In the first place, operation should be avoided in fibrous conditions unless symptoms are troublesome and organic changes are clearly demonstrated. Patients with equivocal findings are usually more comfortable on conservative management than following any type of operation.

When operation is definitely indicated there is a choice between open operation, the use of the cold punch and resection with high frequency currents. We are making more frequent use of the retropubic approach for excision of fibrous contractures of the vesical neck in children in preference to transurethral resection which, in the child, requires an instrument of limited vision and extremely small loop.[4] Total prostatectomy by either the perineal or retropubic route may be the only means of relieving patients who have distressing complaints following multiple resections of the fibrous prostate. Of course, this procedure renders a patient sterile and, in addition, the perineal operation carries a high incidence of postoperative impotence, factors which deserve special consideration in the younger age group in which the fibrous prostate is so common.

[3] Rosenberg, M. L. and Vest, S. A.: Osteitis pubis. J. Urol., **60**: 767–775, 1948.

[4] Young, B. W.: Retropubic approach to vesical neck obstruction in children. Surg., Gynec. & Obst., **96**: 150–154, 1953.

The cold punch is probably the ideal instrument for removal of fibrous bars and contractures, employing precise point coagulation or a hemostatic bag to control bleeding. By avoiding thermal damage the likelihood of additional scar tissue formation is lessened.

When high frequency currents are used some urologists recommend the removal of small quadrants of tissue in preference to rimming the entire circumference of the vesical neck. For example, taking single bites of tissue at 4, 8, 10 and 2 o'clock will free a tight contracture and permit the entire vesical neck to widen into a large aperture. This technique theoretically prevents redevelopment of a small, constricting ring of scar tissue.

If the hypertrophied trigone is obstructive, midline division tends to remove additional obstruction and may reduce postoperative urgency and frequency.

3) *Avoid damaging the urethra.* Improvement in results also depends upon scrupulous care to avoid trauma to the urethra. Urethral stricture frequently accounts for a persistence of symptoms and prolonged pyuria. Many times strictures go unrecognized, especially if they are of large caliber.

Various steps to avoid damaging the urethra are 1) to use a resectoscope of appropriate size, 2) to perform external meatotomy, internal urethrotomy or perineal urethrotomy whenever indicated, 3) to lubricate the urethra profusely, 4) to prevent urethral spasm by producing adequate anesthesia, using curare when indicated and 5) to select a urethral catheter of sufficiently small caliber for postoperative drainage.

Despite every precaution, it is well to be on the alert for the development of a urethral stricture, which may not become obvious until several weeks following operation. The duration of catheter drainage should be shortened as much as possible to lessen the incidence of urethritis. We prefer to remove the catheter on the third or fourth postoperative day.

4) *Consider the condition of the bladder.* It may be advantageous to delay operating on patients with early obstructions until early decompensation occurs. However, in postponing operation the potentialities of damage to the upper part of the urinary tract should be constantly kept in mind. In cases of this type antispasmodic or anticholinergic drugs are usually without effect. Forcible dilation of the bladder has likewise met with failure.

5) *Prevent infection* and, if it develops, treat it intensively. One of the most important steps in reducing postoperative infection is to avoid introducing infection prior to operation. In patients with uninfected urine a urethral catheter or cystoscope should be inserted only when vital information cannot be obtained by other means. Residual urine can be estimated in most instances by the after-voiding film taken during excretory urography. The policy of performing a diagnostic cystoscopy at the time of prostatectomy has considerable merit, especially in patients with a large hypertrophy in whom the danger of infection is most serious. Whenever preoperative urethral instrumentation is employed prophylactic chemotherapy should be administered. As concerns preoperative retention catheter drainage, this is a hazard to be considered just as seriously as that of poor renal function. In recent years we are using preoperative drainage less and

less, considering it more desirable to operate in an uninfected field when there is no serious renal impairment.

Following operation we give the patient broad spectra antibiotics in an attempt to avoid infection and accelerate healing. In the event that evidence of infection develops specific therapy is instituted, as is indicated by urine cultures and sensitivity tests.

Antibiotic treatment is not without hazard for it may permit such spurious organisms as Pseudomonas and Proteus to flourish after the suppression of ordinary pyogenic strains. Fortunately, these organisms produce few symptoms in the absence of obstruction and usually disappear from the urine without specific chemotherapy within a few weeks.

Postoperatively we use scrupulous care to avoid introducing infection through the urethral catheter. For irrigation we use a closed system and irrigate as infrequently as possible.

6) *Hasten separation of slough.* We have considered methods for accelerating débridement of slough to promote healing in the prostatic fossa. Streptokinase and streptodornase mixtures (Varidase) have a fibrinolytic action and are used widely to accelerate the separation of slough elsewhere in the body. They have also been used successfully following prostatectomy for dissolving clots in the bladder[2] and may have an application following resection.

Obviously there is a tremendous overlap and interdependence of the various factors which lead to poor results. When one considers the zone of necrosis from high frequency currents and the presence of a urethral catheter, both of which lead to almost inevitable infection, conditions seem far from propitious. However, if the measures outlined are followed the untoward sequellae may be considerably reduced. A well executed resection, supplemented by appropriate antibiotic therapy, will minimize the slough, facilitate prompt healing and contribute to the avoidance of serious infection.

SUMMARY

An experimental and clinical investigation is reported which assesses the factors responsible for the poor results following transurethral prostatectomy. The causes of poor results are discussed under three categories: 1) factors inherent in the method, 2) individual variations in operative technique and 3) the influence of the pathologic lesion. On the basis of the studies various expedients and measures are advocated to improve the results; specifically, to make the proper choice of prostatectomy, to use the optimal operative technique, to avoid damaging the urethra, to consider the condition of the bladder, to prevent infection and to hasten separation of slough. If the measures outlined are followed the untoward sequellae may be considerably reduced.

Appreciation is expressed to Dr. Lincoln E. Moses of the Department of Public Health and Preventative Medicine, Stanford University School of Medicine, for assistance in statistical analysis of the results.

2201 Webster St., San Francisco 15, Calif.

IMPORTANCE OF FROZEN SECTIONS IN EVALUATING PROSTATIC NODULES

ORMOND S. CULP AND JOHN R. McDONALD

Section of Urology, and Division of Surgical Pathology, Mayo Clinic, Rochester, Minn.

It has been axiomatic that precise diagnosis is a prerequisite of rational therapeusis. Many ingenious techniques have been devised for histologic study of palpable nodules in the prostate but only perineal exposure of the gland affords direct access to the entire troublesome posterior lamella. Biopsy via this route, therefore, should have the greatest potential for indicating unequivocally the bona fide candidates for so-called radical operations.

The combination of frozen-section examination and simultaneous prostatectomy of appropriate type has no parallel in other diagnostic or therapeutic schemes. This theoretically ideal one-stage procedure has attained only limited popularity, however, owing to the exacting technical details of perineal dissection or to skepticism regarding the diagnostic value of frozen sections.

Our study was undertaken in the hope of answering two pertinent questions: 1) Can carcinoma of the prostate, especially early lesions, be diagnosed with consistent accuracy from frozen sections alone and 2) is histologic confirmation of clinical impressions necessarily important when selecting patients for radical prostatectomy?

The survey has been limited to palpable nodules within the prostate of individuals whom we considered suitable candidates for the radical operation. This assured inclusion of those lesions which are usually most confusing to pathologists as well as urologists.

Each prostate was exposed perineally and a generous sample was taken from the indurated portion. In some instances the entire lesion was excised. Multiple biopsy specimens were examined when the induration was less impressive after the gland had been exposed and when the first piece of tissue was reported benign.

PREPARATION OF FROZEN SECTIONS

The frozen sections were prepared according to a standard technique, as follows: The fresh piece of tissue is placed on the stage of a Spencer freezing microtome and frozen with carbon dioxide. Sections are cut with an average thickness of 10 to 15 microns. One of these is floated on the surface of cold tap water and then transferred on a glass rod to Terry's polychrome methylene blue stain for a few seconds. The section is washed in fresh tap water and mounted on a glass slide with a cover slip over it. The mounting medium is tap water.

Sections prepared in this manner will deteriorate because the fluid evaporates and the stain fades on exposure to light. Usefulness of the preparation can be prolonged by sealing the edges of the cover slip with lacquer to prevent evaporation of the water. Most sections, however, can be preserved for only a little more than twenty-four hours.

It is especially important that the sections be fairly thin and well stained, and some experience with the technique of making fresh frozen sections is required. We routinely have residents in pathology and residents from the various surgical specialties cut our fresh frozen sections and find that after one to three weeks of experience, they make reasonably good fresh frozen preparations. A very essential part of the technique is the use of a sharp knife. Our knives are sharpened after a day's use during which they cut 40 to 50 preparations.

INTERPRETATION OF FROZEN SECTIONS

The interpretation of preparations is made by means of low power and high power microscopy.

The carcinomas of the prostate which give the pathologist difficulty in diagnosis are those which produce well-formed acini. When the acinus 1) loses its papillary projection and 2) becomes smaller and when 3) the cytoplasm of the cell takes up fat and is therefore clear, one should suspect carcinomatous changes. It is not sufficient that only two of these criteria be fulfilled. We have found it necessary for all three to be met in order to make a foolproof diagnosis of carcinoma (fig. 1).

Another very helpful feature to look for in fresh frozen sections, as well as fixed sections, is the presence of collars of tumor cells around nerves. Because the piece of tissue under discussion is usually removed from the posterior lamella of the prostate, nerves and vessels are very readily demonstrated.

In order to become expert in the diagnosis of carcinoma of the prostate from fresh frozen sections, one must be familiar not only with the appearance of numerous carcinomas of the prostate in fresh frozen sections but also with the appearance of benign conditions which mimic carcinoma, such as metaplasia of

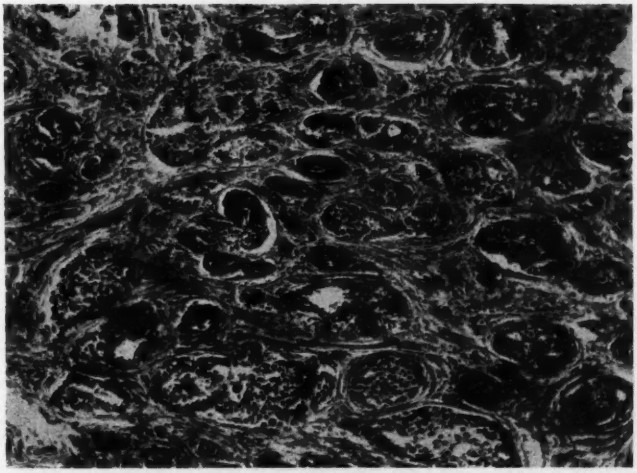


FIG. 1. Adenocarcinoma of prostate. Note small lumina, lack of papillary infoldings and cells with clear cytoplasm (fresh frozen section stained with Terry's polychrome methylene blue; ×95).

prostatic epithelium. The pathologist who examines questionable lesions of the breast and little else by the fresh frozen technique is probably inadequately prepared to interpret prostatic lesions by this method.

ACCURACY OF METHOD

The foregoing morphologic criteria were used to interpret frozen prostatic sections from 45 patients. In 40 cases the diagnosis was carcinoma while in 5 instances a benign condition was reported.

Each piece of tissue used for frozen section was examined later by means of conventional fixed sections. *The original diagnosis was confirmed in every case.* Finer details of the permanent sections merely permitted more precise differentiation between grades of malignancy. Twelve patients had grade 1 lesions, 26 had grade 2 lesions, and 2 had grade 3 lesions.

Admittedly, this is a small series but consistency of this degree has not been unique. All our surgical specimens are examined routinely by both frozen and fixed techniques, and the final diagnosis rarely differs from the provisional one.

IMPORTANCE OF METHOD

More important than any vindication of the frozen-section technique as a dependable diagnostic procedure is the question of whether or not such studies have significant clinical value, and this we attempted to determine in our study.

The 40 patients with positive biopsy specimens were treated by radical perineal prostatectomy. All are now impotent, even though 21 are less than 60 years of age, 1 is only 45, and the average age for the entire group is 59.5 years.

Four of the 5 patients with benign lesions had no urinary difficulty and the remainder of the prostate was not disturbed. The fifth patient underwent simple enucleation of adenomas because of obstructive symptoms. The ages of these 5 individuals varied from 41 to 64 years with an average of 55.4 years. None has noted any change in his libido or potentia since the operation.

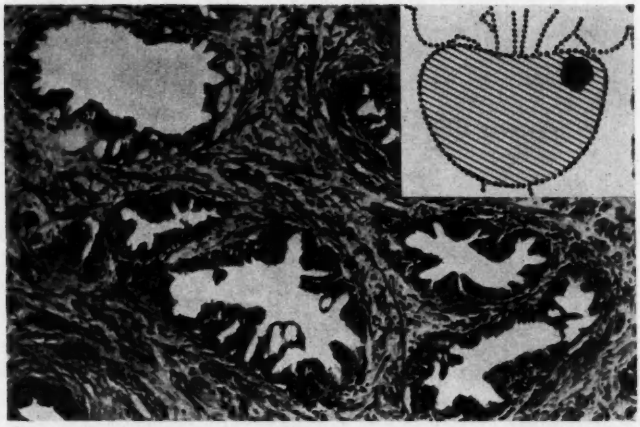


FIG. 2. Case 1. *Inset*, diagram of unenlarged prostate showing indurated nodule at base of right lateral lobe. Photomicrograph of biopsy specimen taken from nodule shows benign hyperplasia (hematoxylin and eosin; ×65).

It is obvious, therefore, that sacrifice of the entire prostate entails a definite physiologic price which may not be too great for possible "cure" of a potentially lethal disease but one which the unafflicted surgical victim may not accept too philosophically, especially when appropriate preliminary measures could have circumvented this stigma. To date we have found it difficult to be reconciled to prophylactic total prostatectomy.

On the other hand, more serious errors may be perpetrated when patients are denied radical prostatectomy merely because biopsies have not been employed to maximal advantage. Even in retrospect we were unable to discern any special clinical features whereby patients might have been selected for operation more discriminantly. Without adequate biopsies there would have been inevitable errors of omission as well as of commission. Included in our series of 45 cases were several striking examples of potential pitfalls in the simple palpation of prostates.

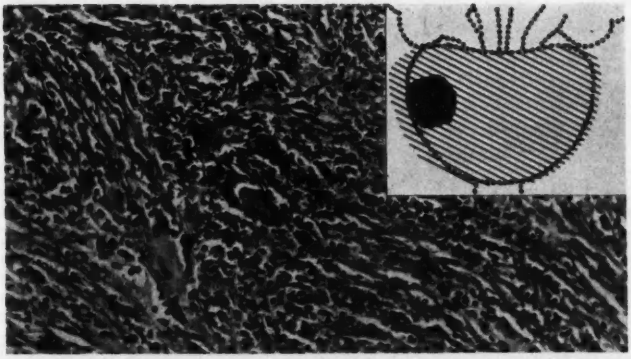


FIG. 3. Case 2. *Inset*, diagram of prostate showing slightly enlarged left lobe which contains a palpable nodule. Photomicrograph of biopsy specimen taken from nodule shows granulomatous prostatitis. Note giant cells (hematoxylin and eosin; ×160).

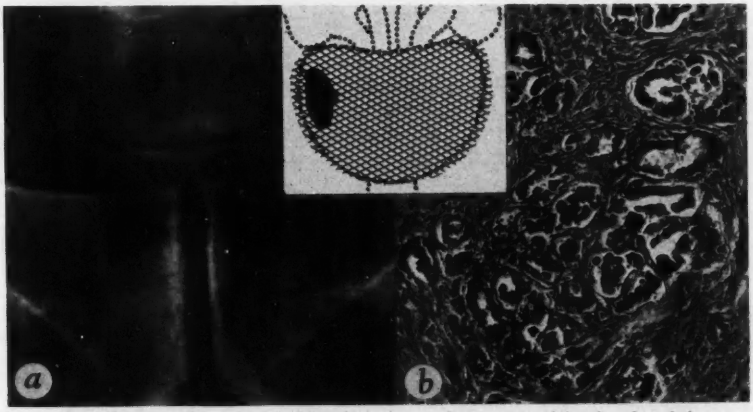


FIG. 4. Case 3. *Inset*, diagram of diffusely indurated prostate with a hard nodule near the left lateral border. *a*, Plain roentgenogram showing multiple prostatic calculi. *b*, Photomicrograph of biopsy specimen taken from nodule showing adenocarcinoma (hematoxylin and eosin; ×135).

ILLUSTRATIVE CASES

Cases 1 and 2, to follow, were thought to be classic examples of early prostatic malignancy.

Case 1. A patient, aged 41 years, had been treated successfully for lymphosarcoma of the neck and had a stony-hard nodule near the base of the right lateral lobe of an otherwise normal prostate. Biopsy showed benign hyperplasia (fig. 2).

Case 2. A patient, aged 57, had an area of third degree induration in the slightly enlarged left lateral lobe of the prostate. Frozen-section examination revealed a localized area of granulomatous prostatitis (fig. 3).

In the other 3 instances of benign disease the condition proved to be either benign hyperplasia or granulomatous prostatitis despite multiple biopsies.

The hazards of hasty interpretation are illustrated by case 3.

Case 3. A 57-year-old patient with diffuse induration in the prostate had been

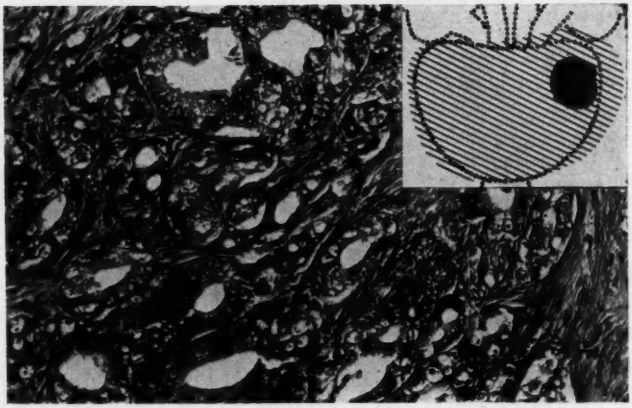


FIG. 5. Case 4. *Inset*, diagram of prostate showing palpable nodule on right. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×160).

FIG. 6. Case 5. *Inset*, diagram of slightly enlarged prostate showing ill-defined nodule on right side. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×110).

found to have prostatic calculi, and no treatment had been advised. One area on the left was much firmer than the remainder of the gland. Frozen-section examination disclosed adenocarcinoma (fig. 4).

The importance of continued observation is demonstrated by case 4.

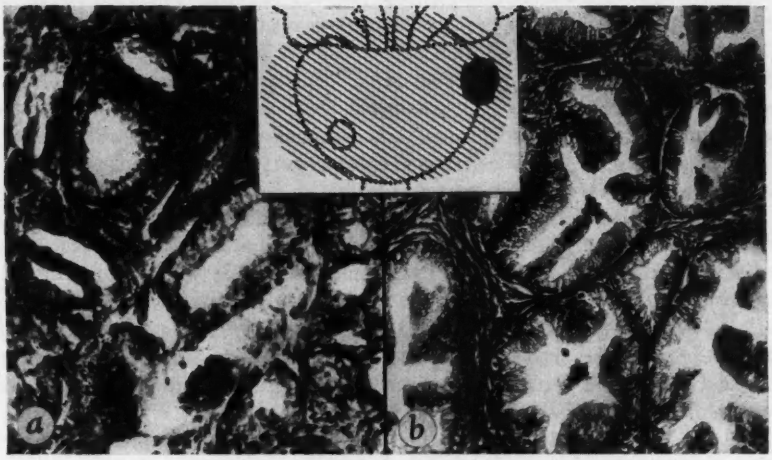


FIG. 7. Case 6. *Inset*, diagram of diffusely enlarged prostate showing markedly indurated nodule on right and site of random biopsy on left. *a*, Photomicrograph of biopsy specimen taken from nonindurated left side showing adenocarcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from indurated portion showing benign hyperplasia (hematoxylin and eosin; ×115).

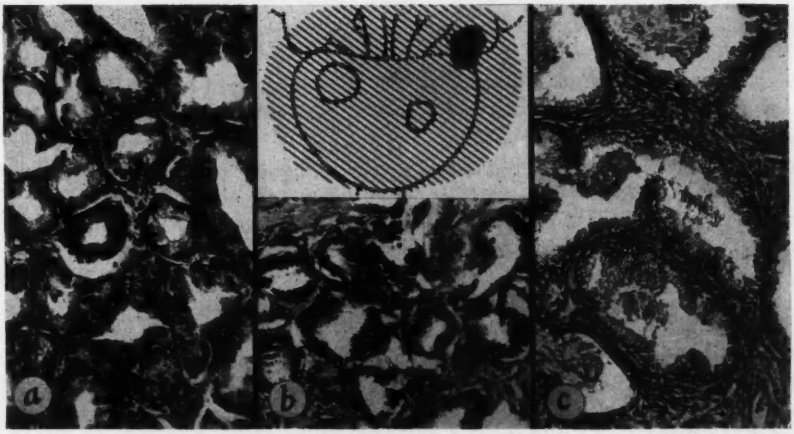


FIG. 8. Case 7. *Inset*, diagram of enlarged prostate showing hard nodule near base of right lobe, and sites of biopsy of left lateral lobe and right side of posterior lamella. *a*, Photomicrograph of biopsy specimen taken from center of enucleated left lateral lobe showing carcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from right side of posterior lamella showing adenocarcinoma (hematoxylin and eosin; ×150). *c*, Photomicrograph of biopsy specimen taken from palpable nodule showing benign hyperplasia (hematoxylin and eosin; ×100).

Case 4. A patient, aged 63, had a smooth, movable nodule in the right lateral lobe which was examined annually for eleven years. Between the 1951 and 1952 examinations it became larger and firmer. Frozen-section examination disclosed adenocarcinoma (fig. 5).

Case 5 offers irrefutable proof that the degree of induration can be a fallacious index and that more prostates should be subjected to biopsy.

Case 5. A rather ill-defined nodule, only slightly firmer than the remainder of the gland, was noted in a patient aged 63. Most examiners interpreted it as a small adenoma. Frozen-section examination showed adenocarcinoma (fig. 6). Four similar doubtful lesions proved to be adenocarcinomas.

The elusiveness of prostatic cancer and the importance of multiple biopsies are demonstrated by cases 6 and 7.

Case 6. A patient, aged 69, had prostatic enlargement and typical obstructive symptoms. The right lobe contained an extremely hard nodule. Frozen-section examination disclosed only benign hyperplasia. A similar but random biopsy of the unsuspected left side of the gland revealed adenocarcinoma (fig. 7).

Case 7. A patient, 70 years of age, had severe obstructive symptoms. At the base of the right lobe of the prostate there was a very firm nodule. Frozen-section examination showed benign hyperplasia. The enlarged lateral lobes were enucleated. Routine frozen-section examination of the specimen revealed an unsuspected carcinoma within the tissue from the left lobe. The remainder of the prostate was removed and a second area of adenocarcinoma was found in the posterior lamella (fig. 8). Perhaps multicentric growths of this type account for some of the conflicting opinions regarding the behavior of so-called occult lesions.

SUMMARY AND CONCLUSIONS

In 45 cases no discrepancies were encountered between diagnoses based on frozen sections obtained by direct perineal biopsy and those made after study of permanent sections from the same tissues. If frozen-section biopsy had not been performed, 5 patients would have lost their entire prostates needlessly and would have been destined to be impotent, while 5 other patients with true carcinomas probably would have had no operation. If multiple biopsy specimens had not been examined, 2 additional patients would have been left with carcinoma after simple enucleation. The results of this study, therefore, seem to warrant the following conclusions:

Carcinoma of the prostate can be diagnosed with consistent accuracy from frozen sections, providing the biopsy is adequate. Difficulties with the method are probably due to inexperience.

To initiate or deny irreversible, definitive therapy solely because of impressions derived from the palpation of the prostate is fraught with considerable hazard. Not all nodules of third degree induration are malignant and many carcinomas are only slightly indurated. Histologic confirmation of clinical diagnoses is imperative if radical prostatectomy is to be employed judiciously.

The combination of direct frozen-section biopsy and simultaneous radical perineal prostatectomy, when indicated, still seems to be the logical treatment for early carcinoma of the prostate.

THE USE OF SOLUSPONGE IN PROSTATIC SURGERY

JOHN N. ROBINSON

From the Squier Urological Clinic, Presbyterian Hospital and College of Physicians, New York, N. Y.

Even with the advances in the development of new absorbable hemostatic materials the control of bleeding after removal of the prostate is not always wholly successful.

"Solusponge is a physical modification of pure starch, possessing exceptionally high and innate hemostatic properties. These properties are due to the innumerable cell-like spaces which expose a great surface area to the shed blood, and also to the breakdown of sugar products which are released in high concentration on its surface. Such concentrated sugar solutions cause agglutination of red corpuscles and facilitate the clotting action".[1]

The use of Solusponge in Urology was first described by Ritter who carefully studied both the hemostatic and absorptive properties.[2]

The methods of using it and its effect on postoperative care will be discussed. Solusponge comes unsterilized in rectangular strips measuring 2 by 2 by 8 mm. and in two sizes of cones which can be sterilized by autoclaving. Any of the antibiotics or liquid hemostats can be used to impregnate the starch before use.

Our best results were obtained by using one of the following methods. After the prostate has been removed and the arterial bleeding controlled and the prostatic capsule contracted, then the rectangular strips are packed so as to completely fill the prostatic bed. These dry strips are placed in the bed and firmly held in place for one minute with pressure. If a Foley catheter is used the strips are used in a similar manner with one strip on each side around the catheter. The balloon is then blown up and pulled down compressing the sponges in the prostatic cavity. It is held in place by traction on the catheter to the leg for 3 to 4 hours.

A careful study of 75 cases in which Solusponge was used shows in general very few differences as compared with other hemostatic agents.

Two cases had mild secondary hemorrhages controlled by transfusions. The sponge had apparently been ejected into the bladder when the pressure had been relieved.

Two other cases passed small gelatinous pieces of tissue for 8 to 13 days after operation. They were washed out of the bladder by irrigation through a catheter but in no instances were calculi found or was operation for removal necessary. Analysis of these tissues showed no evidence of starch granules and to date no cause has been found for their production.

A comparison with other methods of controlling bleeding shows equally good hemostasis and there is no difference in the number of type of spasms occurring in convalescence. Wound closure is not hastened. Severe postoperative hemorrhage has not occurred in this series.

In summary, Solusponge is a useful hemostatic agent in prostatic surgery. It is easy to handle and is an effective agent in control of bleeding. Its suitability for impregnation with antibiotics may be of value.

180 Fort Washington Ave., New York 32, N. Y.

[1] Pamphlet describing Solusponge.

[2] Ritter, J. S., and Bloomberg, H.: Solusponge as a hemostatic agent in Urology. J. Urol. 67: 543–546, 1952.

DISCUSSION

DR. HUGH J. JEWETT (Baltimore, Md.): I should like to comment especially on the paper of Dr. Culp. It is true that many nodules of the prostate are malignant, but it is also true that a number are benign. In over two hundred perineal exposures for suspected carcinoma at the Brady Institute, 89 per cent of the cases were found to be malignant and 11 per cent benign.

Radical perineal prostatectomy is followed by perfect urinary control in 75 per cent of the cases and slight stress incontinence in 13 per cent leaving 12 per cent of the cases sufficiently incontinent to require some sort of a device. About 98 per cent are totally impotent. These figures should emphasize the desirability of accurate histological proof of malignancy, before proceeding with what may turn out to be an unnecessary operation. Such caution will prevent unfavorable publicity as well as a possible lawsuit, for no sexually active male will relinquish lightly his sexual function.

I would differ with Dr. Culp in one respect about the frozen section. When the diagnosis is clear cut, the frozen section is valuable and entirely satisfactory, as in the photomicrographs which he has shown. But in a borderline case, even though the frozen section may be thin and beautifully stained, the diagnosis will be in doubt, and greater reliance can be placed on the permanent paraffin sections. In a case of this sort, it is better to return the patient to his room and tell him and his family that you cannot be sure of the final diagnosis until the permanent sections are completed in 48 hours. This protects the surgeon as well as the patient.

Nodules in the prostate which seem to be circumscribed on rectal examination are not always localized. Of thirty-one well circumscribed and delineated nodules in our series, only five were histologically strictly localized. In twenty-six the carcinoma had grown more or less diffusely throughout the entire prostate, and in eleven of those twenty-six, carcinoma cells had already reached the perivesical tissues. A finding therefore of a circumscribed nodule on rectal examination does not always mean that a cure can be obtained by radical perineal prostatectomy.

DR. DAVID M. DAVIS (Philadelphia, Pa.): I would like to congratulate Dr. MacDonald on his very fine paper. I think he has made it very clear that the proper criteria for the mortality and morbidity, both pre- and postoperative in prostatic surgery, must be brought up to date, and that every one of us must be strictly on his toes, because 4 and 5 per cent mortalities are no longer permissible.

With regard to Dr. Culp's paper, it seems to me that those of us who have been speaking in favor of this "so-called" (as Dr. Culp properly says) radical operation—which, nevertheless, has a fine record of suitability in properly selected cases—have often felt like missionaries who are abused and thrust out on too many occasions.

At the Mid-Atlantic Section this year, Col. James C. Kimbrough presented an excellent paper showing as the result of his insistence over many years, the officers of the United States Army have been given routine yearly rectal examinations,

and the circumstances of these examinations have been so well set forth that for a period of years, 54 per cent of all cases of carcinoma of the prostate entering the Walter Reed Hospital have been found suitable for radical operation.

These radical operations have been performed, and as far as can be told, the results are about as reported in all other series of such operations, namely, approximately 50 per cent living and apparently well at the end of five years. Of course, other people claim that patients live five years with hormonal treatment and orchiectomy. Perhaps that is so, but in the meantime these unfortunates are taking pills all the while, they are undersexed, they have painful breasts, and they know that they still have cancers within them; whereas many of the radical cases have forgotten all about it, and, while even if they may have recurrences ten or twelve years from now, yet for the moment—five years after operation—they are leading normal lives, not only physically but psychically.

Gentlemen, it seems to me that it is time we made up our minds about this thing. We have been talking about how good the operation is, but it has only been done on a corporal's guard of people, only, and regrettably, an insignificant proportion of those who might benefit from it if brought to surgery at the proper time.

Many people have wished that a campaign could be started to inform the general medical profession and the public about this situation, just as they have been informed everywhere about the status of the early diagnosis and treatment of cancers of the cervix and cancers of the breast. Cancers of the stomach and rectum are now receiving similar treatment.

No such thing has been done with cancer of the prostate. Why? Because we urologists have stumbled and fumbled with the proposition. We have fought amongst ourselves. Too many of us have thrown cold water on the whole proposition, and I don't understand why. There is nothing difficult about this operation. Any opposition to it is purely emotional.

Certainly, men such as all of those I see before me now—who do not hesitate to do cystectomies or uretero-intestinal transplants, or division of isthmuses of horseshoe kidneys, and other operations which are ten times as difficult as a radical perineal prostatectomy—shouldn't hesitate to do it if they think it is a good thing to do.

I think Colonel Kimbrough said there were 11,000 or 12,000 deaths from carcinoma of the prostate each year in this country. Let us suppose that by proper indoctrination of the profession and the public we manage to get 54 per cent of those cases operated upon at a proper stage in the development of their cancers. That would be 6,480 operations each year. If 50 per cent were living and apparently well at the end of five years, that would be 3,240 people who had received very considerable benefits.

At the present time I think it is no exaggeration to say that less than 5 per cent of the carcinomas of the prostate are brought to radical operation at a suitable stage in the progress of the disease. That means that at the most optimistic estimate possibly 600 receive the benefit of the operation each year. If 50 per cent of the 600 are living and apparently well at the end of five years, we have 300 people

who have received the benefit of this procedure, instead of a possible number of 3,240.

The difference between 300 and 3240 is 2940. Have we any right to deny those nearly 3,000 people the benefits which might come from this procedure?

DR. BEN D. MASSEY (Pasadena, Calif.): I enjoyed Dr. Weyrauch's thoughtful paper, and I have just one or two passing comments. He states that it is very difficult to find the surgical capsule, or at least the point of separation, transurethrally, as compared with the suprapubic approach for separation of the adenoma.

For a good many years we have always attacked the gland from the top, at the 12 o'clock position and cut it loose from its supports, then bluntly catch it with the knife and separate it just as if one were using the handle of the scalpel. Then, as it separates, remove the tissue. In that way it is very easy to follow the so-called surgical capsule. One will not then tend to get into the venous sinuses. Or one can go through the remaining parts of the fibrous capsule, if you wish to do so.

Dr. Weyrauch is one of the few who have said that the attack of the contractures of the bladder neck is most difficult by transurethral resection, as far as the results are concerned. I think that is a hundred per cent true. We have had much better results with them in the last few years since we have been using the isotonic solutions, and we have lost some of the fear of invading the capsule.

It is my feeling that the fibrous neck should not only be incised, but that it should be severed. Actually, extravasate these people by cutting the trigone loose at its lateral attachments to the bladder neck (and in those quadrants go well out beyond the fibrous ring) and then lastly split the trigone down to the point where we can begin to see the blue color of extravesical tissue. This is the final maneuver. We can do it safely only with the isotonic solutions.

Then we leave our catheter in about 72 hours rather than 48.

On the question of biopsies, I back up Dr. Jewett's statement about the practicality of doing radical operations on anyone in whom we do not have an absolute diagnosis of cancer. I think if we made the mistake on one individual out in California, we would probably be out of the practice of Urology within the following year. From a practical standpoint, we have found it is almost impossible to get our pathologists to commit themselves definitely on frozen sections with any degree of accuracy.

We have excellent pathologists, two who are professors of Pathology in two of the schools of southern California, but we still cannot get them to commit themselves on frozen sections.

We have tried to get around that in two ways. We have found that the punch or the needle biopsy has been working rather satisfactorily for us. I do not care to discuss whether that is a safe or satisfactory method of doing it as far as the spreading cancer is concerned. I wonder if it may give us the same results that the biopsies of the breast have done in the past, in which delayed operation has been done upon the breast. But it has been a practical way of getting around the question of frozen biopsies and then being able to attack the prostate with some sense of security, knowing that we are dealing with carcinoma.

Also, I do feel that with the exception of the occasional small nodule which is up at the base of the seminal vesicle, one can biopsy almost any nodule in the prostate by transurethral resection.

DR. WYLAND F. LEADBETTER (Boston, Mass.): What I have in mind may be largely theoretical, but it seems to me that we are assuming the biopsy of the prostate does no harm.

It just doesn't appeal to me to expose a lesion through the perineum and incise the limiting membrane of that cancer.

It seems to me that one should be willing to accept the fact that there are a certain number of patients in whom one can't be certain about the diagnosis, even if biopsies are made. I feel that if I had a questionable carcinoma of the prostate, I would not want the lesion biopsied. In the first place, the prostate is different from the breast. In the breast one can excise the whole area that has been traumatized to get the biopsy, but in the prostate one cuts into a lesion which is then exposed directly to the wound, which cannot be excised. The performance of a radical perineal prostatectomy is a traumatic procedure.

Without doubt, some of the cases of local recurrence must be due to spillage of cells. Obviously, if one is dealing with a very sclerotic type of carcinoma, there isn't great opportunity for cells to be disseminated, but if the cancer is more cellular—and this is a microscopic disease—I believe one can disseminate cancer.

I never had any experience with disseminating cancer by needle biopsy until this last year. I have one case that developed a nodule in the perineal wound proved by excision to be prostatic carcinoma which I am sure did not arise by direct extension from the prostate. It represented a group of cells spilled from the needle.

I would like to introduce the thought that the biopsy of a prostatic lesion may be a dangerous procedure. I believe one has to recognize the fact that one can't make a hundred per cent diagnosis. I have never found a patient on whom I have done a total prostatectomy, or radical prostatectomy, who was subsequently proved not to have cancer, who wasn't so happy about it that there was no problem connected with it.

I think it is a matter of frankness with patients, explaining the situation to them and doing what you think is right. Of course, if you think that biopsy is right, that is one thing, but I think we ought not to regard biopsy of the prostate as a perfectly harmless procedure.

DR. JOHN L. EMMETT (Rochester, Minn.): May I ask Dr. Lich a question concerning osteitis pubis? We have seen very little of this complication at the Clinic because we have done almost no retropubic prostatectomies. Recently, however, we encountered a case of osteitis pubis, the result of a left ureterolithotomy done elsewhere about 3 months previously. The incision had been carried well down over the symphysis pubis. Previous to admittance to the Clinic various types of treatment, including deep roentgen therapy, cortisone and ACTH, had given no relief. No abnormality could be demonstrated by x-ray. Relief was finally afforded the patient by means of a left obturator nerve crush. I would like to ask Dr. Lich if any new treatment has been developed for this

troublesome complication or is the procedure of obturator nerve crush still the treatment of choice?

Dr. Roger C. Graves (Boston, Mass.): I agree so heartily with Dr. Culp in his paper concerning the management of early carcinoma of the prostate, and with the very excellent remarks of Dr. Davis concerning this subject, that I feel impelled to continue this discussion just a minute or two longer, to disagree with my very good friend, Dr. Leadbetter. It would be too bad to discourage us from making biopsy examinations of the prostate by the perineal route because of any idea that the disease might be disseminated thereby. I have had the same feeling, many times, that Dr. Leadbetter has expressed, but I have never known of any ill effect resulting from such a biopsy through an open perineal wound. If the site of biopsy is very carefully walled off at the time the tissue is taken; if the area of the biopsy is thoroughly electrocoagulated—and usually we follow this with the application of alcohol—there is very little practical likelihood of spreading cancer at that point.

I believe it is true, also, that prostate cancer is seeded in the surrounding tissues with considerable difficulty because this particular tumor—as I have been told by pathologists—requires its own substrate to grow readily. It is easy for me to believe this, because in all of the cases of perineal surgery for cancer of the prostate that I have seen through the years, I have seldom, if ever, seen a recurrence in the scar.

Dr. Clyde L. Deming (New Haven, Conn.): I would like very much to support Dr. Culp's paper, and to oppose, slightly, my friend from Boston.

After doing perineal prostatectomies for 30 years, I have not seen in that period a local recurrence after a total prostatectomy or after a nodule biopsy. That is my answer to the problem of doing perineal prostatectomy biopsies.

I have been asked a question several times with regard to this problem: If you should do a perineal prostatectomy and get back a return from your biopsy specimen that it is benign tissue rather than carcinoma, and then in three or five days your regular pathological report shows cancer, what would you do with that case? In those cases I go ahead within a period of three weeks and do a radical perineal prostatectomy. If you allow a longer period to intervene, your perineal section will be difficult, but if you do it within a period of three weeks, one can go ahead and do a radical perineal prostatectomy.

I would like to commend Dr. MacDonald for his paper, and would ask you not to lose sight of one thing in his paper which I think some of the younger men might miss. Why does he show such a marked improvement in recovery in the last few years? I don't believe it's surgery. I don't believe that we are much better surgeons than some of the surgeons of 30 years ago, but I do believe the secret lies in the thorough preparation of cases, and in the thorough knowledge of the renal function, and the nonprotein nitrogen studies. Of course, that includes the cardiovascular studies, also. There is a tendency among some of the younger men to slip over part of this phase of our work in prostatectomy.

Dr. Fletcher H. Colby (Boston, Mass.): The papers in this symposium showed a great deal of work behind them.

Dr. Davis's remarks were good for our souls, and I am glad he made those remarks.

I can't help but add my support to Dr. Culp's remarks.

Last year I reported a hundred total prostatectomies for suspected early carcinoma of the prostate. In our biopsies through perineal exposure and frozen section, the pathological report was accurate in 91 per cent, which is not a bad average, considering the difficulties that the pathologist is up against with his frozen sections, and the difficulty of making a diagnosis of carcinoma of the prostate even from permanent paraffin sections at times.

In our cases, I have not seen at any time that biopsy done through the perineum or by the Silverman needle could fairly have been the cause of local tumor spread. Perhaps it is because the cancer cells find a great deal of difficulty growing in the media from which they have been transported.

Dr. C. D. Creevy (Minneapolis, Minn.): I would like to ask a question about carcinoma of the prostate.

Our professor of Surgery, Dr. Wangensteen, makes as radical an attack on abdominal cancer, I think, as anyone in the world with the possible exception of Dr. Brunschwig. He has taken occasion several times to "needle" me in public because I have resolutely refused even to consider pelvic evisceration for carcinoma of the prostate which is obviously beyond the stage of total prostatectomy, and I would just like to know whether there is anyone here who feels as he does, that it should be done.

Dr. Gilbert J. Thomas (Santa Monica, Calif.): Mr. President, I hope your suggestion that these papers be turned in promptly will be followed. Much material here which we have had in abstract form, we will want to go over again. We want to read the papers, and those of us who are interested in teaching will find much teaching material here for undergraduates.

Dr. Weyrauch has shown us that transurethral resection of the prostate gland may be done better by means of the so-called punch instrument which, however, is not a punch as the term implies. It is a round knife that removes as much material as does the actual electric loop but does not cauterize. Many of us who have been doing punch operations for a long while know that our results have been better than with the use of the loop.

I hope you will have the opportunity to come to California. When you do, visit Dr. Weyrauch's laboratory. He is an intensive but practical worker as is evidenced by the tremendous amount of material that he has brought to us today.

At the University of California at Los Angeles, under the direct supervision of Dr. Willard E. Goodman, who is a protege of Dr. W. W. Scott's, we have been conducting a research problem in regard to the diagnosis of cancer of the prostate gland. As has been mentioned here, I think we urologists should first teach our students methods of diagnosis which is more important than methods of treatment.

We have been doing needle biopsies as an office procedure on carcinoma suspicious cases to determine its efficacy and then doing perineal exposure biopsies and then comparing the sections made in these two ways.

One surgeon has made all the needle biopsies and during the last 24 examinations he has been a hundred per cent right. We are not discontinuing to check needle biopsies by the perineum; however, a surgeon trained in this technique can make a correct diagnosis of the presence of cancer in the prostate gland by this method.

Our experience with frozen sections has not been so good as that of Dr. Culp. We have been surprised in a few instances in which we have removed sections from palpably suspicious areas to find them negative. The wound was closed for a week or until the routine sections were ready and these were positive.

We always take two or more biopsies from other than those palpably suspicious areas. In two instances, evidence of cancer was found in contralateral lobes and other areas of a prostate gland that had a palpably suspicious area. When the pathologist's routine or frozen sections diagnoses are equivocal, the urologist who has other data concerning the lesion makes the diagnosis. We are of the opinion that the surgeon who has all the data concerning the patient and the lesion, if trained in pathology, can and should make the diagnosis.

Dr. Culp says that the resident on the service prepares the sections, but he didn't say whether Dr. McDonald, a pathologist, makes the diagnosis. We look at our own sections, and if we are not sure, we close the patient's perineum temporarily and wait until we get a routine section, as Dr. Graves has mentioned, which takes 48 to 52 hours. Then if it is positive, we do a perineal prostatectomy, a total prostatectomy.

Dr. Wyland F. Leadbetter (Boston, Mass.): I thought I might mention total prostatocystectomies performed for more extensive carcinoma of the prostate. We have not done pelvic evisceration. My experience to date would not indicate that it was necessary.

I think I have done six complete prostatocystectomies of a radical type with gland dissection. One of those patients now has gone more than four years without any sign of recurrence. Another has gone over three years. The others have had recurrences, but the interesting thing is—with reference to implantation of cells in the wound (another direct observation that I can make) that in the abdominal wound of one of these patients who died there was a large mass of carcinoma which has proved by biopsy to be carcinoma of the prostate. That is just another isolated instance, but it happened.

I might give you the history of one case that has gone almost five years. This patient was seen by Dr. Vincent Vermooten at Fort Sam Houston in 1943. He had an extensive lesion at that time which was judged too extensive for radical perineal prostatectomy. He had orchiectomy and stilbestrol therapy from that time until 1947. At the end of 1947, when I saw him, he had difficulty of urination and bilateral hydronephrosis, and a large pelvic mass which involved the triangular ligament.

At that time we had exhausted what amounted to palliative therapy. He was young, 52 years of age, a retired colonel from the Air Force, and anxious that we do everything possible for him.

I operated upon him first using a perineal approach during which I dissected the

triangular ligament out, because there was involvement by disease and freed the prostate. I then went in above and did a complete prostatectomy, cystectomy, and gland dissection, and bilateral uretero-enterostomy. There were no positive glands.

The patient made an uneventful recovery, and he has had no trouble from his uretero-enterostomies, and now, five years after operation—I see him every year—there is no sign of recurrence or metastasis, although that case would ordinarily be considered much too extensive for any operative procedure.

Another man I mentioned had a similar situation, though not quite as extensive, but one positive gland was found. He has gone for four years now without evidence of recurrence and without orchiectomy or stilbestrol therapy.

The third patient had a recurrence in his wound, as I said. He also had a peculiar lymphatic recurrence, in that it developed in the inguinal nodes and in his retroperineal nodes above the level of dissection. He lived for three years after that, which I think was probably better than could have been accomplished any other way.

I am not advocating radical surgery for this type of case, but I think it is true that it isn't always the size of the lesion that is important but rather the pathological potential of the particular lesion. I am sure that if we could individualize such cases and pick out some that are—although rather extensive—of low potentiality of growth, we could utilize this technique to advantage.

Dr. Robert Lich, Jr. (Louisville, Ky.): With reference to Dr. Emmett's question, the treatment of osteitis pubis, I may say that we felt very fortunate to have had only two individuals in whom discomfort was prominent. In one of these patients we considered an obturator crush, but the patient refused further surgery.

In both of our cases we used x-ray, but I question whether or not it altered the course appreciably. As far as any new therapy for osteitis pubis is concerned I am not acquainted with anything that has been shown of value consistently.

Dr. Henry M. Weyrauch (San Francisco, Calif.): Concerning osteitis pubis, we have seen dramatic results following the administration of cortisone in two cases. I don't know whether you consider that routine treatment or not, but we have certainly found it to be spectacular in those two instances.

Dr. Massey called attention to the treatment of the trigone. We think that is tremendously important, and have discussed it in the complete paper.

I would like to summarize, then, as to just what one does for a fibrous prostate.

In the first place, I think the thing to do is to avoid operation if at all possible. If the patient is just a borderline case, it would be better to carry him along conservatively. If intervention is indicated, I think cold knife excision is probably the proper treatment, and we are already using that in a few cases. That answers a question Dr. Herbst asked me, as to whether I would use the cold punch. I think that it is fine in appropriate cases.

As to open operations, we don't like the perineal in these younger individuals, because we haven't yet learned Dr. Culp's secret of preserving potency. Maybe we are more virile out there in California, I don't know, but when we operate on

the perineum we quite often lose sexual potency, and for that reason we don't like to do the perineal operation, which is ideal as far as curing the symptoms goes.

We do have the alternative of the retropubic approach. We agree a hundred per cent that the suprapubic prostatectomy is no operation for the fibrous gland. We use the retropubic approach now almost exclusively in children and have found it ideal in contractures of the vesical neck. We make a longitudinal incision through the prostate and vesical neck, and excise a very deep wedge posteriorly—which we can do with impunity, and as Dr. Massey, have no fear of extravasation. We close the longitudinal incision transversely, leaving a very wide orifice.

DR. ORMUND S. CULP (Rochester, Minn.): I am reasonably sure that many of us could have written the script for this discussion ahead of time. It is a foregone conclusion that everyone here has his own prejudices as to how prostates should be treated, whether they be benign or malignant.

I appreciate the comments by all of the discussants. It is perfectly obvious that we can disagree without being disagreeable.

Regarding Dr. Thomas' comments, I am frank to say that we are relying upon the interpretations of four full-time surgical pathologists. However, we generally look at the sections ourselves, for our own edification, and many of the fellows become exceptionally proficient during the course of their training.

Dr. Jewett thinks that we disagree. We do not. It was not my intention to imply that somewhere in Minnesota there are crystal balls which make a diagnostic procedure infallible. It is quite possible that we may have errors in diagnosis the next time we employ a frozen section. I merely wish to defend a procedure which I think has been maligned unjustly. Most individuals can become proficient in the interpretation of fresh frozen sections, providing they take enough interest in the method and employ it frequently enough to improve their own diagnostic acumen.

PRESIDENT SCHOLL: That concludes our scientific program.

Holding office in this organization, as I have, is the high spot in any doctor's life, as it was in mine. I am certainly duly appreciative, all the way through.

The Homestead is a fine place to have the meeting, and there is a mellow fellowship about this crowd which seems to have grown a little better in the last few years. It was always good, but it is high now.

There is one thing that occurs to me as I look down through the years—it seems that the men are getting younger every year. Unquestionably.

The greater part of the success of this meeting unquestionably goes to the know-how and the zeal and the industry of our retiring Secretary. He is now retiring after making seven Presidents appear very efficient, giving them excellent programs. I think we'll give him a rising vote of thanks for the seven years of work he has done.

(The audience arose and applauded.)

DR. HECKEL: Thanks very much, gentlemen. The only thing I can say is that it has really been a great pleasure to have been Secretary of such a fine organization. (Applause)

PRESIDENT SCHOLL: I would also like to extend a vote of thanks to Dr. Higgins. He has been a great help with our program these last few years. He has also made the Presidents look very efficient and able.

Now it is with a little mixed emotions that I relinquish the gavel to my good friend, Dr. O'Conor. We were taken in during the same year, about 27 years ago. We came together that time. We have been coming every year, and we are still traveling together at the present time.

Now I wonder if Dr. Higgins and Dr. Thomas would escort our incoming President to the rostrum?

(The audience arose and applauded as the incoming President was escorted to the rostrum.)

PRESIDENT-ELECT O'CONOR: I could use some of my Celtic tendencies to prolong the session by illustrating how grateful I am for this, which I consider to be one of the greatest honors of my life, but all I can say is that I do appreciate it very much, and will try to do everything that I can to keep this society on the very high plane which it has always maintained during the last forty or fifty years.